ANÆMIA.

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To

DR. S. WEIR MITCHELL,

THIS WORK IS, BY PERMISSION, RESPECTFULLY DEDICATED.

"Semper honos, nomenque tuum, laudesque manebunt,
Quæ me cunque terræ vocant."

PREFACE.

THIS, the first systematic treatise on anæmia published in this country, is a reprint of a series of articles published in THE POLYCLINIC during the past year, and embodies the results of many years' study of the blood and the disorders consequent upon its imperfect elaboration. The statements which it contains are, for the most part, based upon personal observation, and where this has been wanting, upon accepted facts of physiology and pathology. I have endeavored to supply the want of a trustworthy guide to a wide and growing field of research—a want which I myself have keenly felt.

721 Pine Street, June 1st, 1887.

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ANÆMIA.

INTRODUCTION.

The blood holds in solution certain albuminous bodies, of which the principal are serum-albumin, serum-globulin, and fibrinogen, and a number of mineral substances, the chief of which are common salt (sodium chloride) and sodium carbonate. These may be classed as the invisible constituents of the blood, and their investigation belongs to the domain of the physiological chemist. In addition, it holds in suspension certain bodies, the red and white corpuscles, which are open to direct inspection, and may, therefore, be classed as the visible constituents of the blood. The study of these latter, as regards their form, color, size, number and relative proportion, is the province of the histologist, and it is with these properties that we are concerned in this treatise.

The red corpuscles of man are circular disks, with rounded edges and depressed centres. On account of the difference in thickness between

the central and peripheral parts of a red corpuscle, it is impossible that its entire surface can be accurately focused by the microscope at the same time, and, accordingly, when its centre appears bright its periphery is dark, and *vice versa*. The diameter of the human red corpuscle is about $\frac{1}{1\frac{1}{2}\frac{1}{6}}$ of a millimetre, or $\frac{1}{3\frac{1}{2}\frac{1}{0}\frac{1}{0}}$ of an inch. The chemistry of the red corpuscles is quite complex, and, in some respects, still unsettled. The most important ingredient, hæmoglobin, is conspicuous by its brilliant optical properties, and its amount may be most readily determined by these alone. It is the only proteid of the body that contains iron, and the amount of this mineral in the ash of the blood affords a method of determining the amount of hæmoglobin in a given specimen. It is by means of the hæmoglobin in the red corpuscles that the blood conveys oxygen to the tissues. Hæmoglobin is characterized by the readiness with which it absorbs and parts with oxygen. It exists in the blood in two distinct forms: in the arterial blood as oxy-hæmoglobin, and in the venous blood as reduced hæmoglobin. These two forms are readily distinguished by means of the spectroscope.

Hæmoglobin is crystallizable, the crystals being obtained with greater or less ease from the blood of different animals. They may be obtained most readily from the blood of the rat, by simply mixing it with distilled water on a glass slide. Other means employed with the blood of other animals are: alternate freezing and thawing of the blood, the passage through it of electric shocks, of the vapors of ether and chloroform, and the addition of the alkaline salts of the bile. The largest crystals are deposited from blood that is allowed to undergo decomposition. Thus obtained, they are often of enormous size—from three to five centimetres long. This is explained by the supposition that putrefaction destroys substances which are preventive of crystallization. If there is any single element of the body that deserves to be called "vital," it is undoubtedly hæmoglobin. It is universally present, and conveys to the tissues the element, oxygen, that is most essential to the life of the individual, while its diminution below the normal, even when slight, is manifested by various symptoms of functional disorder, and when extreme and long continued, leads to grave and irreparable organic lesions. Its chemical properties are

extraordinary, and apparently contradictory. It is organic and yet crystallizable; it has an eager affinity for oxygen, and yet parts with it on the slightest demand; it is soluble in water, and circulates in the blood without leaving the red corpuscles; and, finally, without losing its identity, it exists in the blood in two distinct forms: in the arteries as oxy-hæmoglobin, in the veins as reduced hæmoglobin. The absence of this substance from the blood in greater or less degree, is at the root of the various forms of anæmia, about to be considered.

The white, or colorless corpuscles, are spherical masses of granular, nucleated protoplasm, having a diameter of 10 μ* or $\frac{1}{2500}$ of an inch. They possess the power of spontaneous movement, and hence are sometimes called amœboid cells, from their resemblance, in this respect, to the unicellular rhizopod, called the amœba. They exist in healthy blood in about the proportion of one white to five hundred red corpuscles. Their specific gravity is less than that of the red corpuscles, and, therefore, if blood be placed in a narrow cylindrical vessel

* The Greek letter, μ, is used as the sign of the micromillimetre, or one-thousandth of a millimetre.

and kept from coagulating by a temperature a little above the freezing point, or by the addition of a saline, such as sodium sulphate, the red corpuscles will collect at the bottom of the vessel, and the white at the top. Owing to their scanty numbers, great difficulty stands in the way of their accurate chemical analysis. Nevertheless, some work has been accomplished in this direction. Their contractile power is probably dependent upon a substance closely resembling the myosin of voluntary muscle. Their nuclei may be isolated from the surrounding protoplasm by the action of gastric juice, which dissolves the protoplasm and leaves the nucleus intact. The latter is composed of a mucin-like substance, containing phosphorus, called nuclein. The minute granules scattered throughout the substance of the white corpuscles are, some of them, soluble in ether and alcohol, and therefore regarded as fat granules; the nature of the granules not thus dissolved is unknown. Glycogen is also contained in the white corpuscles, as may be demonstrated by treating them with a solution of one part iodine, and two parts potassium iodide, in one hundred parts water.

Besides the red and white corpuscles, other morphological elements exist in the blood, concerning the character and function of which there exists considerable confusion. They are the hæmatoblasts of Hayem, identical with the blood-plates (Blutplättchen) of Bizzozero, the microcytes, and the advanced lymph disk or invisible corpuscle of Norris. When blood is examined under the microscope, there may be occasionally observed, and sometimes in large numbers, certain granular-looking masses of irregular shape, the size of which is variable, but may considerably exceed that of the white corpuscles. They are known as Schultze's granule masses. With strong lenses, it is readily seen that they are not granular or amorphous—like the amorphous urates seen in urine—but are composed of distinct and independent individual elements,* which latter are the hæmatoblasts or blood-plates. "They are the elementary corpuscles of Zimmermann, the *globulins* of Donné, the *grains sarcodiques* of Vulpian, and the *granulations libres* of Ranvier. The latter regarded them as particles of fibrin, which serve as centres of coagulation,

* This was first demonstrated by Osler.

just as a crystal of sodium sulphate dropped into a solution of the same will serve as a centre of crystallization."*

These bodies are not, as has been supposed, disintegration products of the white corpuscles, for they may be seen circulating in the blood of transparent tissues, such as the mesentery. Their function is intimately concerned with the production of fibrin.

The microcytes are round or disk-shaped bodies, much smaller than the red corpuscles. They vary considerably in size, their average diameter being 3μ. They resemble minute red corpuscles, and sometimes contain considerable coloring matter. They are very numerous in idiopathic, so-called pernicious, anæmia, while, on the other hand, the granule masses are but scantily present in that disease. Microcytes are also to be found in perfectly healthy blood.

The colorless corpuscle of Norris is a red corpuscle minus its coloring matter. Norris claims that it is a young red disk that has been elaborated in the lymph glands, and has entered the blood by the thoracic duct, and that it gradu-

* The Coagulation of the Blood. F. P. Henry, *Archives of Medicine*, December, 1884.

ally acquires all the properties of a mature red corpuscle. His opponents contend that it is a red corpuscle deprived of its coloring matter by the very manipulations used to demonstrate it. The question is still unsettled.

The functional power of the blood is dependent upon the number and quality of its red corpuscles. When a deficiency exists in either of these respects, the tissues suffer for the want of oxygen—the most important nutritive element of the body. When the degree of anæmia is slight, it may be manifested by symptoms which are not to be distinguished from neurasthenia in its various forms, except by an examination of the blood. The latter affection often co-exists with a perfectly normal condition of the blood. When the anæmia is of higher grade, the want of oxygen—equivalent to want of breath—may not be experienced except upon exertion, of which the amount necessary to produce this symptom is in inverse ratio to the degree of anæmia. In extreme cases, simply raising the head from the recumbent position will suffice to induce breathlessness or even syncope. Even in such extreme cases, the symptoms alone will not suffice for diagnosis,

for there are diseases of which the most prominent symptoms are due to irregular distribution of the blood, a hyperæmia of one vascular district necessarily causing a correlative anæmia of another, while the constitution of the blood is normal. The most conspicuous example of this condition is furnished by Addison's disease, in which, owing to vasomotor paralysis, there is great accumulation of blood in the abdominal vessels and a correlative anæmia of the brain. Here, also, dyspnœa arises upon slight exertion; the muscles are weak and easily fatigued, and in extreme cases, during the frequent exacerbations of the disease, simply raising the head from the pillow is sufficient to induce syncope. Until very recent times, these symptoms of Addison's disease were ascribed by the most eminent authorities to a high degree of anæmia. It is now established that in such cases the constitution of the blood may be normal, and that the symptoms are due to its irregular distribution. Further instances are unnecessary to prove the diagnostic importance of a proper examination of the blood. The presence of anæmia may be guessed at without such examination, and the diagnosis (?) con-

firmed or rejected by the result of the treatment, while the patient, in the meantime, may have been losing what might have been saved by proper methods. Not only the bare presence of anæmia, but its variety and degree, are to be ascertained by examining the blood, as well as its progress under different modes of treatment. In short, no contribution to the clinical history of a case of anæmia deserves to be compared with that derived from an examination of the blood.

METHODS OF EXAMINATION.

These consist in the enumeration of the red and white corpuscles, and the determination of the percentage of hæmoglobin in the former. The instruments used for counting the corpuscles are all constructed upon the same principle, the different modifications being such as are designed to facilitate the rapid counting of the cells, and the easy reckoning of their percentage as compared with the standard of health. A known quantity of blood is diluted with a known quantity of fluid, and in a cell of certain depth and superficies—the latter indicated by squares of a certain size ruled upon an ocular micrometer, or on the bottom of the cell containing the

blood—the number of corpuscles is counted. With these factors—the depth of the cell, its superficies, and the degree of the dilution—the number of corpuscles in a cubic millimetre of blood, for instance, is readily estimated. It is self evident that the more the blood is diluted, the easier is the counting of the corpuscles, and the longer the subsequent calculation. The chief instruments in use for counting the blood corpuscles are the compte-globules of M. Malassez, for a description of which see *Comptes Rendus de L'Académie des Sciences*, Déc., 1872, also *Thèse de Paris*, 1873; the hématimètre of MM. Hayem and Nachet, described in the *Comptes Rendus de L'Académie des Sciences*, 26 Avril, 1875; and the hæmacytometer of Dr. Gowers, of London.

The different instruments for counting the blood corpuscles may be used in combination. Thus, in many of my own observations, I have used Gowers' pipettes with Hayem and Nachet's cell and eye-piece. Thoma and Zeiss (*Hermann's Handbuch der Physiologie*, IV, Bd. I), also, have constructed an apparatus composed of the pipette used with Malassez' instrument,

known as the mixer (*mélangeur*) of Potain, and a cell similar to that of Gowers. The instruments of Gowers and Zeiss are superior to the others mentioned, in that they may be used with any microscope without adjustment for the different objectives employed. The counting is, however, sometimes rendered very difficult with Gowers' instrument, on account of the large size of the squares—$\frac{1}{10}$ of a millimetre. The squares in the cell of Zeiss' instrument are only $\frac{1}{20}$ of a millimetre, rendering the counting a very easy task. Until quite recent times, it was supposed that the quality of the blood could be accurately determined by counting its corpuscles. If these were found below the standard—5,000,000 per cubic millimetre—anæmia was supposed to exist; while, on the other hand, if above this standard, anæmia was confidently declared to be absent. It was apparently taken for granted that the red blood corpuscle was a constant quantity, a unit, containing invariably the same amount of hæmoglobin. It is now thoroughly established that the amount of hæmoglobin in two red corpuscles, from different individuals, may vary as much as 50 per cent., so that the mere number of the corpuscles

does not afford an infallible proof of the presence or absence of anæmia. When the corpuscles are decidedly below the normal average, anæmia, of course, can be determined by a mere count, but even here its degree can only be accurately estimated by determining the percentage of hæmoglobin, the reduction of which is usually greater than that of the number of the corpuscles. It is, however, in those cases of anæmia in which the number of the corpuscles is normal, or even greater than normal, that the superiority of the hæmoglobin test is unmistakably manifested. The writer agrees with Hayem, that, if one had to choose, in cases of this sort, between the two methods, the color test would undoubtedly be preferred.*

The principal point to be determined in an examination of the blood is the functional value of the red blood corpuscles, which bears a direct ratio to the amount of hæmoglobin in each.

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* "Si dans les cas de ce genre, cas d'ailleurs extrêmement communs, on voulait s'en tenir à l'une des deux méthodes d'examen du sang, c'est donc sans hésitation au procédé chromométrique qu'il faudrait donner la préférence." *Recherches sur l'anat. norm. et path. du sang.* Paris, 1878.

As a rule, when the number of blood corpuscles is normal, the amount of hæmoglobin is also normal, or nearly so, but, and this fact determines the value of a color test, there are numerous exceptions to this rule. Thus, Baxter and Willcocks found 6,600,000 corpuscles per cubic millimetre, in a case of typhoid fever, but they contained only 45 per cent. of the normal quantity of hæmoglobin, making their functional value equal to that of 2,970,000 normal corpuscles; so that, in spite of the high figures, the degree of anæmia was great.

Instruments for estimating the percentage of hæmoglobin have been devised by Hayem, Malassez and Gowers, of which the most simple is the globinometer of Dr. Gowers. I have used this apparatus with much satisfaction. It is light, compact, and easily manipulated. The words of its inventor are equally applicable to the instruments of Hayem and Malassez. "The instrument is only expected to yield approximate results, accurate within two or three per cent. It has, however, been found of much utility in clinical observations."

From these introductory remarks, the importance, for clinical purposes, of a proper exami-

nation of the blood is manifest. It is a significant fact that those who, in the course of their practice, make frequent examinations of the blood, encounter cases of disease never met with by others, with perhaps much greater opportunities for observation ; but no more so than that the oculist has become able, by improved clinical methods, to classify cases formerly vaguely known as "amaurosis," into retinitis, choroiditis, atrophy of optic nerve, separation of retina, glaucoma, etc. The wonderful progress of ophthalmology in recent times has been due to the skillful handling of a small mirror, and what we know of blood diseases, is due to the microscope in conjunction with an apparatus which is already regarded as one of its important "accessories." We now proceed to the consideration of our proper subject, Anæmia.

ANÆMIA IN GENERAL.

The term anæmia, signifying an impoverished state of the blood, is to be preferred, both on the grounds of etymology and euphony, to such terms as spanæmia, oligæmia, oligocythæmia, which have been introduced at various times on the plea of greater accuracy. It has, besides, the great advantage of possessing its

exact equivalent in the French and German languages—"*anémie*" and "*anämie.*" All the different varieties of anæmia are characterized by a diminution of the number or value of the red blood corpuscles; that is to say, of the normal amount of hæmoglobin. From a clinical point of view, this is the primary and essential morbid condition. It is supposed and argued that this reduction in the amount of hæmoglobin is preceded by a reduction in the amount of the plasmatic albuminates; but this question is quite as obscure as that concerning the pre-albuminuric stage of Bright's disease. Anæmia is not a neurosis or a functional disorder, as one might suppose, from the loose manner in which the term is occasionally employed, but a systemic condition dependent upon a lesion which can be demonstrated with the utmost precision.

There are certain predispositions to anæmia dependent upon sex, age and constitution. The female sex is more prone to anæmia than the male; and peculiarly so during the pregnant condition, in which, owing to the great demands upon the blood for the nourishment of the fœtus, anæmia is the rule. On the other hand, the female sex is more tolerant of anæmia than the

male, which is partly due to the fact that the life of females is, as a rule, more sedentary. Many women go through a long life without any particular ailment, but are known to possess what is termed a delicate constitution. Being fortunately free from any constitutional vice, no organic disorder develops; nevertheless they are chronic invalids. They are usually treated with excessive consideration by friends and relatives of their own sex, and regarded by the average practitioner as lucrative humbugs. The fact is, that such women are suffering—if such a term may be applied to a condition which brings with it so great freedom from responsibility—from a light grade of chronic anæmia. It is astonishing upon what a small amount of food such persons support a long existence; but it is to be observed that if the income is small the output is still smaller. Many such persons play the rôle of amiable drones in the hive of busy workers. They do not repine at their lot, preferring to bear those ills they have rather than fly to others (the responsibilities of health) that they know not of.

The predisposing influence of age is most marked during youth and advanced life. The

demands of growth during adolescence render the equilibrium of the blood peculiarly unstable. This, also, is more marked in females, in whom the evolution of the sexual system is, as a rule, attended with more systemic perturbation.

Anæmia should, undoubtedly, be classed among the tissue changes known to the histologist as "senile;" indeed, there is excellent ground for believing that it is at the root of those which are most suddenly disastrous, to wit, the degenerations of the walls of small blood vessels. During the inevitable period known as the "decline of life," the system is especially intolerant of nutritive losses. The recuperative power of the blood is impaired. It is just at this period, also, that the diseases attended with such losses are most prevalent; among which are to be reckoned chronic catarrhs of mucous surfaces, such as the pulmonary and vesical; hemorrhoids, ulcers, etc.

Anæmia may be congenital. In 1883, while examining the blood of several new-born children at the Maternity Hospital, I encountered the following case:—

"CASE 3.—Mary C———, born 5.20 A.M., November 5th. Count made 2.30 P.M., Novem-

ber 6th. Child weighed six and three-fourths pounds at birth; labor natural. Number of red corpuscles per cubic millimetre, 3,625,000; proportion of white cells to red, 1 to 145. This case was undoubtedly one of congenital anæmia. The child's only appearance of malnutrition was a shriveled state of the integuments of the feet, and a less rosy color of the skin than normal. For a new-born child, it was decidedly pale. This shriveled state of the skin emphatically negatives the idea of a relative anæmia from excess of fluid. The blood was probably deficient in quantity (oligæmia) as well as defective in quality (oligocythæmia). There was also a decided increase in the number of the white cells. Careful inquiry proved that there had been no hemorrhage from the cord. As possibly bearing upon the congenital imperfection of this child, I may mention the fact that the parents were themselves immature—the father being seventeen, and the mother eighteen years old."* It is possible, also, that the case may have been one of congenital syphilis.

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* See paper entitled "A Contribution to the Study of Icterus Neonatorum," by Frederick P. Henry, M.D. *Archives of Medicine*, October, 1883.

The third cause, above mentioned, as predisposing to anæmia, is *constitution*. No better proof of the existence of such a tendency can be brought forward than the report of the above case of congenital anæmia. An extended series of examinations would probably show that such congenital deficiencies in the composition of the blood are by no means uncommon. Certainly, the widest differences of external appearance are presented by the new-born, from the pale, puny *sickling* of five or six pounds, to the rosy, vigorous child weighing from ten to twelve. With proper care, the puny child may thrive and grow, perhaps, too rapidly, and present every appearance of health, but in after life, under circumstances to which its more vigorous contemporary would rise superior, the *innate* tendency to anæmia will manifest itself. Precisely similar facts are observed with reference to the other tissues of the body. One individual will not only retain his weight, but grow fat upon a diet which another would regard as but little removed from starvation.

EXCITING CAUSES OF ANÆMIA.

It is hard to draw a sharp line between the predisposing and exciting causes of anæmia.

To the writer it seems proper to include among the latter such causes as are equally operative in either sex and at all periods of life; but in such a division no allowance is made for the wide differences in individual power of resistance.

A cause will excite anæmia in an individual with an innate tendency to the disease; while in another, devoid of such tendency, it will not do so, unless long continued or frequently repeated. In the former the cause deserves to be called exciting; in the latter its action is more closely allied to that of the causes called predisposing. Bearing this in mind, the exciting causes of anæmia include hemorrhage and other pathological discharges, sexual excess, insufficiency of food, light or air (bad hygiene), the depressing emotions of grief and anxiety, fever, and, finally, whatever interferes with the digestion, absorption and assimilation of food. It is not pretended that this list is complete, for, as Immermann remarks, "Nearly every morbid process, when it occurs in a severe form, is sooner or later followed by anæmia." It would be tedious to enter at length into even the chief exciting causes of anæmia; but two, which are

the most frequently encountered in medical practice, deserve more than a passing notice. These are hemorrhage and fever. Experiments of Vierordt upon the lower animals—dog, rabbit, guinea pig—show that death ensues promptly, when, after bleeding, the red corpuscles are reduced about fifty per cent. Later observations show that these figures are not applicable to human beings, whose powers of resisting hemorrhage are very much greater. For example, Béhier (quoted by Laache) reported the case of a woman whose blood, after a metrorrhagia, contained but 19 per cent. of the normal number of red corpuscles ; having, theretofore, suffered a reduction of 81 per cent. The woman recovered after transfusion. Laache examined the blood of five previously healthy women who had suffered from profuse hemorrhage, and found the red corpuscles reduced respectively 37, 61, 62, 64 and 68 per cent. In three of the cases there was complete *restitutio ad integrum*, without transfusion ; in one, death occurred from an intercurrent disease, septicæmia ; and in the remaining case, improvement was progressing at the time of the report. It must be borne in mind, however, that the result of a blood ex-

amination after hemorrhage, depends upon the time at which such examination is made. It is self-evident that, if from a quantity of blood outside the body three-fourths be removed, and a sample of the remaining fourth be examined, its centesimal composition will be the same as that of a sample taken from the whole mass. So, also, if the blood in the living vessels be examined immediately after a profuse hemorrhage, its composition will closely resemble that of the entire volume of blood before the hemorrhage. It will not be identical with it, however, for during the progress of a hemorrhage, the lymph, the tissue juices, and any ingested fluids, are rapidly taken up by the blood vessels to restore the blood volume; so that, as Immermann remarks, the immediate effect of a profuse hemorrhage is a "complex dyscrasia, made up of hypalbuminosis, leucocytosis and oligocythæmia." It is no doubt true, in the majority of cases, that even during the progress of a hemorrhage, owing to the diminished vascular tension, the "osmotic current of tissue juices" is strongly directed toward the blood vessels; but I believe there are cases in which, on account of the shock to the system produced by

the sudden escape of a large amount of blood, this current is extremely feeble, or even, for a time, held in abeyance, and in which, therefore, an examination of the blood, immediately after hemorrhage, will show little or no difference in its cellular composition. The following is a case in point:—

On June 6th, 1885, I examined the blood of a woman, Mary L., æt. thirty-two, who, during the preceding four weeks, had suffered from constant metrorrhagia, which, on two occasions, had been quite profuse. I only succeeded at last in stopping the hemorrhagia by the intra-uterine application of Monsell's solution. On June 5th there was still some slight oozing, which had entirely ceased by the 6th, the day on which the examination was made. Number of red corpuscles, per cubic millimetre, 4,600,000. Proportion of white cells to red, 1 to 460.

"As far as the number of red corpuscles per cubic millimetre is concerned (I quote from my note book), and the proportion of white to red, the blood may be considered absolutely normal, but the woman is greatly prostrated, with blanched skin and mucous membranes. The

volume of her blood is evidently greatly diminished."

As studies of the centesimal cellular composition of the blood after hemorrhage, Laache's cases are defective, as he himself admits, on account of the time between the hemorrhage and the first examinations. These were made, respectively, in Case I, on the 20th day after the hemorrhage; in Case II, on the 21st; in Case III, on the 6th; and in Cases IV and V, on the 5th.

The anæmia of fever offers certain peculiarities, to which I have called attention in an article in THE POLYCLINIC for September 15th, 1885, entitled "The Latent Anæmia of Typhoid Fever." These are, in part, dependent upon the loss of water sustained by the system in all febrile affections, and particularly in typhoid, owing to its long duration and intestinal complications. In typhoid fever, which may be taken as a type, notwithstanding the evidences of an impoverished state of the blood, afforded by the profound adynamia and the muscular tremors, an examination during the height of the disease will show, at least, a normal number of red corpuscles. The blood taken from the

finger is of a dark venous hue, does not flow readily on puncture, and is evidently inspissated. The condition is precisely the reverse of that which obtains after hemorrhage, which is a point of some interest, since it has been held, by at least one eminent authority, that a moderate hemorrhage during the course of typhoid fever is not to be dreaded as a complication. This clinical fact, if it be one, may be explained by the tendency of the blood, after hemorrhage, to regain its former volume by the imbibition of water. The therapeutical deduction is to supply fever patients abundantly with water, as was so strongly advocated by the late Dr. J. Forsyth Meigs.

Although the number of red corpuscles in a cubic millimetre of blood may be normal in typhoid fever, their value is decidedly below par. They are deficient in hæmoglobin, so much so, that six million corpuscles may have only the functional power of three million.

In one form of fever, the malarial, recent investigations tend to show that a micro-organism may be directly active in destroying the red corpuscles. These organisms, if such they be, were beautifully demonstrated by Dr. Council-

man, of Baltimore, at the recent meeting of the American Association of Physicians. They occupy the interior of the red corpuscles, and are apparently capable of distinct amœboid movements. That some agency destructive of the red corpuscles is operative in certain cases of malarial fever is proved by the occurrence of hæmoglobinuria as a symptom, which latter is but itself the sequence of a preceding hæmoglobinæmia. The blood corpuscles are destroyed while circulating in the vessels.

SYMPTOMS OF ANÆMIA.

It is customary for medical writers to describe the immediate effects of the sudden escape of blood from the vessels as typical of what they call acute anæmia; but this, in my opinion, is a mistake. As I have elsewhere said: "The symptoms of acute loss of blood, and its frequently fatal termination when not more than one-half the normal amount has been lost, are due to sudden ischæmia of the nerve centres." Anæmia undoubtedly exists, but is not the cause of the immediate symptoms of hemorrhage. These are due to a disorder of the circulation, which may be precisely imitated by the appli-

cation of Junod's boot to one of the lower extremities.

The remote effects of a hemorrhage, that is to say, the condition of the patient when the nervous system has recovered from its shock and the circulation has regained its equilibrium, may be taken as typical of acute anæmia. The chief of these are pallor of skin and mucous membranes, muscular weakness, vertigo or syncope, on exertion, or even on assuming the upright position, and a small, soft, frequent and excitable pulse. In addition, there is thirst, anorexia, or an appetite that is irregular and fanciful. The digestion is feeble and readily disordered. There is a prevailing sense of cold, and yet on slight exertion the skin becomes flushed and perspiration breaks out. The temper is apt to be peevish and irritable, and the normal control of the emotions is impaired. While the temperature, upon the whole, is lowered, irregular pyrexia, to which the term "anæmic fever" has been applied, is commonly observed in the severest forms of anæmia. The cause of this fever has given rise to much discussion, and the explanation offered by Immermann seems to be the most plausible. It is

that, owing to the extreme reduction of the nutritive properties of the blood, the tissues suffer to such an extent as actually to undergo a spontaneous decay or necrobiosis, which is attended with the evolution of heat, as is always the case "when chemical compounds of a more stable kind are generated from such as are less stable."

Hæmic, systolic, cardiac murmurs, and a musical murmur (bruit de diable) in the jugular veins, are among the physical signs. In high degrees of anæmia there is great emaciation, which is generally masked by œdema. Hemorrhages from mucous surfaces, particularly in the form of epistaxis, and into the retina, are of common occurrence. A fatal termination is generally ushered in by a mild form of delirium, which may be for days preceded by a condition of lethargy, from which the patient is readily roused to full consciousness, but relapses into the lethargic state as soon as the effort to attract his attention is abandoned. The last remarks are only applicable to certain fatal forms of anæmia into which there is reason to believe an anæmia simplex may sometimes be converted. If an anæmia of high degree, whether it originate in hemorrhage, fever, or what not, becomes

chronic, all the organs of the body, and among them, of course, those concerned in blood making, will suffer from malnutrition, so that a condition which was at first what is termed functional, may eventually become organic; that is to say, dependent upon lesions to which it has itself given rise.

ANATOMICAL CHARACTERS.

The anatomical characters dependent upon a marked and long-continued deficiency of red corpuscles, are dryness and translucency of the tissues and fatty degeneration of the heart, intima of the arteries, renal and gastric epithelia, and the hepatic cells. In the heart, the papillary muscles are chiefly affected, especially those of the left ventricle, and the morbid change may be detected by the naked eye in the form of minute, yellowish streaks, which have been called "tabby mottling," or "tabby-cat striation." The retinal hemorrhages are dependent upon degeneration of the vessel walls and, in one form of anæmia, upon this, in connection with a plugging of the vessel affected, with white blood corpuscles. The blood is seen to be less than normal in quantity and of a lighter color

than natural. In well-marked cases, it is of a light pink color, resembling water in which beef has been washed, and the hue which it imparts to linen is sometimes a pale yellowish pink, which would hardly be recognized as a blood stain. Notwithstanding the deficiency of red corpuscles, and the consequent pale tint of the blood, the muscles, even in the highest degrees of anæmia, are often found of a deep red color, and the adipose tissue of a rich yellow.

DIAGNOSIS.

The lighter grades of anæmia merge imperceptibly into health. In city residents, even of the well-to-do classes, whose occupation is attended with considerable mental work and its inevitable anxiety, anæmia is the rule rather than the exception. A number of corpuscles, not below 5,000,000 per cubic millimetre, of which the richness in hæmoglobin, as determined by Gowers' hæmoglobinometer, does not fall below 90 per cent., may be considered normal. This being understood, the lightest grade of anæmia would be expressed by the following formula:—

N. (number of red corpuscles per cubic m.) = 100
H. (percentage of hæmoglobin) . . . = .80
V. (value of each corpuscle) . . . . = $\frac{8}{10}$

An individual whose blood condition would be expressed by these figures, might show little or no departure from health, and be aware of none. I have several times found such figures in young men whose blood I have examined for the purpose of comparing one counting instrument with another. In the above example, N. is normal, say 5,000,000, but these 5,000,000 corpuscles possess only four-fifths the normal percentage of hæmoglobin, and are, therefore, functionally equal to 4,000,000 normal corpuscles.

Anæmia, as a rule, is not clinically appreciable until the hæmoglobin represents between three and four million corpuscles per cubic m. The actual number of red corpucles may be five, or even six, million per cubic m., but their real value is sixty, or even fifty, per cent. of the normal. This degree of anæmia is attended by both signs and symptoms, such as pallor, a tendency to vertigo, flushing of the face, perhaps tinnitus aurium, muscular fatigue on slight exertion, backache, irregular appetite, and a capricious, captious temper. Such a condition might be merely functional, or secondary to the early stage of some organic affection, such as

Bright's disease, diabetes mellitus, carcinoma, phthisis, etc.

The next grade of anæmia is that in which the real value of the corpuscles is between two and three millions. In this degree, the percentage of hæmoglobin may be much greater than in the preceding, owing to the fact that now the corpuscles are decidedly reduced in number. It is a familiar fact to all students of blood diseases that, as the number of corpuscles diminishes, the percentage of hæmoglobin increases, until in the severest forms of anæmia —those termed pernicious—it may equal or exceed, even double, the percentage of red corpuscles. A reduction of both number and value of red corpuscles is much graver than a mere diminution of value. A number as low as 3,000,000 generally indicates a serious state of affairs, and may depend upon a more advanced stage of one of the diseases above mentioned, or upon one or other of the diseases of the blood-making organs, to be considered later.

The highest grades of anæmia are those in which the real value of the corpuscles varies between 500,000 and 2,000,000 per cubic m. Such figures are generally the expression of

diseases of the blood-making organs—spleen, lymph glands, bone marrow—or of that form of "*anæmatosis*" to which the term pernicious has been justly applied. An apparent paradox is met with in these intense forms of anæmia, namely, that 500,000 corpuscles may contain as much hæmoglobin as is usually found in one million. When this is the case, it is due to the fact that the average diameter of the corpuscles is decidedly above the normal. This increase in size may possibly be a conservative provision on the part of nature, but the fact remains that increased size and altered shape (poikilocytosis) of the red corpuscles must be regarded as of very grave significance. An average diminution in the size of the corpuscles is generally combined with an increase in their number, a set of conditions commonly observed in that form of anæmia called chlorosis.

PROGNOSIS.

The prognosis of anæmia in general has been sufficiently hinted at in the preceding remarks; but it may be well to emphasize the fact that an anæmia *per se* is never grave until distinct anatomical alterations in the red corpuscles—

alterations of size and shape—are manifested. The prognosis of secondary anæmias is involved with that of the primary disease.

TREATMENT OF ANÆMIA IN GENERAL.

On account of the general prevalence of Anæmia, its preventive treatment is of the utmost importance. The great majority of individuals who are "run down" in health, or suffering from "nervous exhaustion," which they attribute to overwork, are simply, as before said, more or less anæmic. Overwork is the unfortunate scapegoat whose erratic conduct renders him an easy prey to both physician and patient. Work may be rather regarded as a raw, nutritive material, which is usually prepared and served in an underdone condition. There may be exceptional cases in which anæmia is justly attributed to overwork alone, but the writer has never seen one. There is a careless way of regarding this matter which leads to inaccurate statements. For instance, if the hours of work encroach upon those of sleep, it is the want of sleep, as much as the excess of work, that is to blame for the resulting anæmia. If the irrational worker neither

takes the time to eat or digest his meals, his anæmia is due to inanition or indigestion. If he finds, or imagines, that the steady use of tobacco, coffee and alcohol is helpful in the kind of work he is performing, it is just possible that his habits are alone to blame for his impaired physical state.

As this is not a treatise on hygiene, I shall not stop to indicate the amounts of food, air, exercise and sleep essential to preserve the health of the average man, woman or child; but I cannot refrain from pausing to condemn a prevalent error. There appears to be a widespread delusion in the minds of young men that muscular strength and bodily health are synonymous terms. This is true, indeed, but only to the extent that a *certain amount* of muscular strength coincides with the healthy condition. There is a limit in each individual—a Rubicon—the very attempt to cross which is attended with danger. The story of the man who began by lifting the calf, and continuing to do so each day, ended by lifting the cow, is one of those plausible lies which only serve to enhance the beauty of truth by showing how a germ of the latter may give an air of *vraisemblance* to a

tissue of falsehood. It is a pitiful sight, relieved only by its absurdity, that of a young, slender stripling exhausting himself in vain efforts to become an "athlete." Out-door sports are excellent for the growing boy, but heavy gymnastics should be reserved, as a rule, for those who have attained their full growth. The boy will defeat his object of becoming a strong man by practicing them too early. Let him possess his soul in patience. As the fisherman says, in La Fontaine's fable :—

> " Petit poisson deviendra grand,
> Pourvu que Dieu lui prête vie."

The curative treatment of a case of anæmia is, in part, determined by its causes, and includes the control of hemorrhage and other pathological discharges ; the removal from an unfavorable hygienic environment; the administration of a proper amount of nutritious food, and the suppression of causes which interfere with its digestion and assimilation. In many inveterate cases, in which cure is still possible, this result cannot be attained without weeks, perhaps months, of persevering treatment. A complete control of the patient is essential, and to this

end, the seclusion insisted upon by Dr. Weir Mitchell is of great importance, for by it an important obstacle to recovery is at once removed, to wit, the demoralizing sympathy of injudicious friends. Excellent results have been accomplished by the means so judiciously employed by Dr. Mitchell, namely, rest, seclusion and passive exercise in combination with the diet and medication adapted to the peculiar exigencies of the case. This method of cure has been elaborately explained by Dr. Mitchell in his well-known work, entitled, "Fat and Blood," and is doubtless familiar to the medical men of this country. I have seen a number of cases of chronic anæmia whose treatment by this method has been attended with the happiest results. I have also seen it fail, as is to be expected where everything fails, namely, in the secondary anæmia of malignant disease, and also in certain advanced cases of pernicious anæmia, in which there were marked alterations in the size and shape of the red corpuscles, as well as extreme diminution of their number.

The advantages to be derived from a thorough employment of the so-called rest cure are within the reach of few, and in the majority of cases

our main reliance is on drugs. The chief of these are iron, arsenic, the mineral acids and cod-liver oil. Hayem also reports the successful employment of ferrocyanide of potassium in cases of decided anæmia. The preparations of iron are so numerous that, supposing them to be of equal value, one might well be at a loss to select from among them. This, however, is by no means the case, and I will, therefore, indicate those which I consider the best. In pill form nothing has given me more satisfaction than the formula of Blaud :—

℞. Ferri sulphatis,
Potassii carbonatis, āā gr. iss. M.
Sig.—One, or more, after each meal.

To obtain the best effects of a ferruginous preparation, it is often necessary to give it in large doses, and the above is no exception to this rule. It may be pushed, if well borne, to the extent of three pills thrice daily. The lactate, the pyrophosphate, the malate and Quevenne's powder, are all excellent preparations of iron. Strychnia, quinia and arsenic may be advantageously combined with the iron. The latter preparation is best given in the form of

Fowler's solution. In addition to its specific action upon the skin, arsenic has for a long time been recognized as possessing a general beneficial action in certain states of impaired nutrition, which had caused it to be classed among the agents known as "eutrophic." There is no doubt that much, if not the whole, of this favorable effect is due to the increased amount of hæmoglobin in the blood, which results from its administration. Arsenic is specially indicated in anæmias of malarial origin, although its use is by no means limited to these forms.

The treatment of secondary anæmias is largely influenced by the nature of the primary affection. As a general rule, arsenic will be found of service in those forms of secondary anæmia in which there is a state of congestion or catarrh of the gastro-intestinal mucous membrane. Osler reports good results from its use in the anæmia of heart disease, the "*cachexie cardiaque*" of French writers. In the causation of this form of anæmia, the obstacle to absorption presented by the engorgement of the gastro-intestinal veins is an important factor.

In cases with a syphilitic history, the mercuric

chloride may be usefully administered with iron, as in the following formula:—

℞.	Hydrarg. chlorid. corrosiv.,		gr. j	
	Tinct. ferri. chlorid.,		ʒ ij	
	Glycerin.,		℥ ss	
	Aquæ,	q.s. ad.	℥ iij.	M.

Sig.—One drachm after each meal. The dose may be gradually increased to two drachms thrice daily.

The ferrocyanide of potassium recommended by Hayem is worthy of trial, on account of its endorsement by so distinguished an authority on the physiology and pathology of the blood. He begins by giving one gramme (about gr. xv) daily, in two powders, and gradually increases the dose until six grammes, in six powders, are given.

Transfusion is a measure which has been so often adopted as a *dernier ressort* that it has fallen into discredit. If any benefit is to be derived from transfusion, it is certainly not when the patient is moribund. After the sudden escape of a large amount of blood, the natural process of restoration may be best imitated by the injection into a vein of a normal

saline solution (0.6 per cent. NaCl.), the amount of which must be determined by the effects upon the patient; or the following formula of Hayem for intra-venous injection in cholera, may be employed :—

℞.	Distilled water,	1 litre
	Sodium chloride, pure,	5 grammes
	Sodium sulphate, pure,	10 grammes. M.

Sig.—Filter and inject slowly at a temperature of 38° C. (100.4° F.)

When the object of transfusion is not so much to overcome the effects of sudden ischæmia of the nerve centres as to introduce a gradual improvement in the patient's nutrition, defibrinated blood should be employed.

It has been pointed out that when the respiration is greatly embarrassed, the injection into the vessels of an additional amount of reduced hæmoglobin, such as exists in venous blood, may only make matters worse by adding to this embarrassment, and so accelerate a fatal ending. In such cases the blood to be transfused should be taken from an artery. Quite recently the injection of defibrinated blood into the peritoneal cavity and into the subcutaneous

connective tissue has been practiced with apparent benefit. The dangers attendant upon the transfusion of *heterogeneous* blood are well known. It should never be used. Milk has been transfused successfully in a few rare instances, but for this purpose is greatly inferior to defibrinated blood. It is apt to occlude the vessels, many of its globules being much larger than the largest white corpuscles. If used, it should be boiled, in order to destroy the bacteria which are almost sure to be present.

VARIETIES OF ANÆMIA.

Anæmias are properly classified with reference to their origin. The nutritive fund of the blood is continually drawn upon in the processes of nutrition, and if the demands are inordinate, as in fever and hemorrhage, the resulting anæmia may be justly ascribed to undue waste. Under this head a large number of anæmic conditions might be grouped. A large proportion of the remainder might, with equal propriety, be attributed to inadequate supply of nutritive materials, due either to absolute want of proper food, or to its imperfect digestion and absorption. There would still remain a number of cases in which both of these causative factors

are so intimately combined that it is impossible to decide which of them deserves the greater etiological importance. A division based upon such physiological data as above pointed out, although desirable, is, with our present knowledge, altogether inadequate. Like so many classifications in other departments of medicine, it is not ample enough to cover our ignorance of the subject. In a previous contribution* to the literature of anæmia, I advocated a division of its different forms into essential and symptomatic, and gave the following explanation of my reasons for so doing:—

"By essential anæmia, I mean those forms of the affection that are associated with disease of the cytogenic organs, or with congenital malformations of the vascular system, namely, the lymphatic, splenic and medullary anæmiæ, and chlorosis; and by symptomatic anæmia, those forms of the disease associated with affections of non-cytogenic organs which interfere with nutrition, such as febrile anæmia, the anæmia of phthisis, cancer, Bright's disease, the anæmia of heart disease—cachexie cardiaque of Andral—the anæmia of lead poisoning and of inani-

* Cartwright, Essay, 1881.

tion. Malarial and syphilitic anæmia occupy the border line between the two classes. When recent and dependent upon an acute attack, they may come under the head of febrile anæmia, but when chronic, they are frequently essential, the one generally of the splenic, the other of the lymphatic, variety. These afford interesting examples of the conversion of a symptomatic into an essential anæmia, and it is held by the writer to be highly probable that they are not the only instances of such conversion."

The time that has passed since the above paragraph was written has only served to strengthen the opinions it contains, more especially that concerning the conversion of one form of anæmia into another. At present, however, I prefer the terms "primary" and "secondary" to "essential" and "symptomatic," because they are more widely employed and more in accord with our general medical nomenclature.

In addition, I am in favor of a third division, to include those forms of anæmia due to the destructive effect of toxic substances upon the blood corpuscles, and would suggest for them the term *toxanæmia*.

Anæmias of parasitic origin are so important in certain countries (and perhaps more so in our own than we suspect) as to merit separate classification.

The following classification is offered, in the belief that it is one under which all the different varieties of anæmia may be appropriately grouped :—

I. PRIMARY ANÆMIAS.

Chlorosis.
Lymphatic anæmia (Hodgkin's disease).
Splenic "
Leucocythæmia.
Pernicious anæmia.

II. SECONDARY ANÆMIAS.

Anæmia of fever.
" hemorrhage.
" phthisis.
" heart disease.
" cancer.
" syphilis, etc.

III. TOXANÆMIAS.

Anæmia of lead poisoning (saturnine anæmia).
" arsenic "
" arseniuretted hydrogen poisoning.
" phosphorus poisoning.
" nitric oxide "

IV. PARASITIC ANÆMIAS.

Anæmia caused by Anchylostomum duodenale.
" " Bilharzia hæmatobia.
" " Filaria sanguinis.
" " Plasmodium malariæ.

CHLOROSIS. ANÆMIA OF PUBERTY.

With the advent of puberty comes the most sudden and imperative demand upon the blood that is encountered during the normal life history of the individual, and this is superadded to the continued demands of growth, which is most active at this period. It is, therefore, not surprising that an anæmic condition is common at this time of life; the wonder is that it is not the rule. The developmental impulse of puberty will rouse from their dormant existence any congenital imperfections of the blood such as were described in an early part of this work.

A great deal of confusion surrounds the subject of chlorosis, which is partly due to the fact that statements made by well-known authorities in times when the blood was but rarely examined, have been repeated ever since by writers upon the subject. The researches of Johann

Duncan, in 1867,* demonstrated that in chlorosis the red corpuscles may be normal in number, while their value—the quantity of hæmoglobin they carry—is greatly reduced. In Duncan's cases—three in number—the percentage of hæmoglobin was 0.3. 0.31 and 0.37, the normal standard being 1. While there can be no question of the originality and value of Duncan's demonstration that the coloring matter of the red corpuscles may be reduced without a corresponding diminution of their number, I am convinced that such a condition is not peculiar to chlorosis or any other form of anæmia. In fact, in one of the cases upon which his celebrated observations were made there is room for doubt as regards the diagnosis, owing to the fact that the patient had a splenic tumor.

By chemical analysis of the blood, in cases of chlorosis, a condition has been detected which is thought by some to be pathognomonic. Becquerel and Rodier, and Quinquaud have found a normal proportion of albuminates in the plasma of chlorotic blood, while in the blood of anæmia in general, they are said to be di-

* Sitzungsbericht der K. Acad. der Wissensch. in Wien. B. lv, 1867.

minished. Indeed, the first two observers have found a condition of hyperalbuminosis. Immermann, in his excellent article in Ziemssen's Cyclopædia, adopts this as the distinguishing trait of chlorosis, which he regards as an affection *sui generis*, and deprecates any attempt to "merge it in the great ocean of anæmia." He holds that the blood in this affection is deficient in hæmoglobin alone without any corresponding diminution in the albuminates of the plasma.

Quincke, in view of the discrepancies between his own examinations of the blood in cases of chlorosis and those of Duncan, concluded that there must be at least two kinds of chlorosis—the one with a normal number of corpuscles deficient in hæmoglobin; the other with a diminished number of corpuscles, which may be either normal or deficient with regard to their hæmoglobin.* Laache has examined the blood of cases presenting the typical picture of chlorosis, and found it normal in every respect. He

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* "Es muss daher verschiedene Chlorose geben, die eine mit normaler Zahl aber verringertem Hb-gehalt, die andere mit verminderung der Zahl derselben wobei der Hb-gehalt des einzelnen normal oder ebenfalls vermindert sein kann."—*Virchow's Arch.*, 1872, B. liv., p. 537.

proposes for these anomalous cases the term, *pseudochlorosis*. He contends that they are cases of chlorosis, because their symptoms are identical with that affection, and quotes with approval the following sentence from the thesis of Moriez: "L'hématologiste diagnostiquera l'anémie et ne pourra pas diagnostiquer la chlorose; ceci est affaire au clinicien." I may say, in passing, that I entirely dissent from this view of the subject. Virchow has endeavored to place chlorosis upon a distinct anatomical basis by demonstrating, in fatal cases, an imperfect development of the heart and blood vessels. He has found the aorta of a full-grown woman so small as barely to admit the little finger, and its coats, while preserving their elasticity, were much thinner than normal. In addition, degenerative changes in the intima were often met with. With this diminished calibre of the arterial system, the heart may be either normal in size, subnormal, or hypertrophied. When it is recalled that the blood vessels and the red corpuscles are derived from the same embryonic layer—the mesoblast—the bearing upon the pathology of chlorosis of a congenital hypoplasia of this portion of the

skeleton becomes manifest. Virchow's doctrine has not, however, met with general acceptance. One of the most important functions of the arterial system is its power of adaptation to varying volumes of blood, and in chlorosis, to employ the words of Coupland, "no proof has been given that the diminution in size of the vessels has not followed upon diminution in the total quantity of blood." With reference to this subject, Fagge remarks: "I believe that such affections are not congenital, but due to endocarditis occurring in childhood. Thus it seems to me that the hypoplasia of the aorta, instead of being itself a primary defect, is but a secondary result of the valvular lesion. I am not, therefore, disposed to attach much value to Virchow's observations as they stand at present."

From the above remarks, an idea may be obtained of the obscurity surrounding the subject of chlorosis from an anatomical and chemical standpoint. The same is true with regard to its clinical history. The most various conditions of different organs and systems have been described as more or less symptomatic of this affection. The heart has been found abnormally small in some cases, abnormally

large in others. The genital system is sometimes imperfectly developed; at others, its development exceeds the normal limits. Sometimes amenorrhœa exists, and may either precede or follow the anæmic symptoms. On the other hand, a chlorotic menorrhagia has been spoken of. The number of red corpuscles has been found normal in some cases, increased or diminished in others. Immermann's view that the blood of chlorosis is peculiar in that it is only deficient in hæmoglobin, the plasmatic albuminates being undiminished, is not generally accepted, for "it has not been proved, except in a few cases of pernicious anæmia, that the serum albuminates are diminished in other forms of idiopathic anæmia besides chlorosis."* With regard to Laache's cases of *pseudochlorosis*, there can be no doubt that the symptoms were due to irregular distribution of the blood, especially to the supra-diaphragmatic portion of the trunk. A blood of good quality, if not properly distributed, may give rise to some of the gravest symptoms of anæmia, such as pallor, syncope, cardiac palpitation, feeble pulse, etc.

* Coupland. Gulstonian Lectures on Anæmia. *Lancet*, April 16th, 1881.

This is well seen in certain cases of Addison's disease.

The confusion in which the subject of chlorosis is involved is due to the persistence in regarding it as a disease *sui generis*, distinct from all other forms of anæmia. The truth of the matter appears to me to be simply this: At the time of puberty there is an urgent physiological demand upon the blood, which is complied with by vigorous individuals without detriment to the organism. The ordeal of puberty is safely passed. In less vigorous, but still sound, healthy organisms, a decided degree of anæmia, one calling for treatment, declares itself at this time. Finally, in those with any congenital tendency to anæmia, whether this may have been due to general malnutrition during intra-uterine life, or to a special hypoplasia of the vascular system (the mesoblast), the anæmia of puberty is intense. The case is a typical one of chlorosis.

The term chlorosis is too convenient to be readily abandoned, for under it has been, and will be, included many sins of diagnosis. This is a questionable advantage, and the term should only be used to express an anæmia occurring

at the age of puberty and in the great majority of cases, in the female sex.

DIAGNOSIS.

The diagnosis of chlorosis is included in that of anæmia in general. There is nothing special with regard to the blood to mark it as a distinct disorder. In mild cases there may be a normal number of blood corpuscles, and a reduction in the amount of hæmoglobin which may be but 60, or even 50, per cent. of the normal. In severe cases the number of corpuscles and the percentage of hæmoglobin are both reduced. In the well-marked case of a young lady æt. 17, whose blood I recently examined, I found the following figures :—

No. red corpuscles per cubic millimetre, 2,690,000.
Color (hæmoglobin) . . . . . 32 per cent.

The percentage of red corpuscles (hæmic unit), as compared with the normal (5,000,000), was 54, so that the value of each corpuscle was only $\frac{32}{54}$ of the normal, making the 2,690,000 corpuscles found equal to 1,594,080 normal corpuscles.

The corpuscles were smaller than normal and perfectly circular in outline. The white cells

were not increased. With reference to the mere number of the red corpuscles in chlorosis, Hayem gives 3,520,000 as the mean of eighteen counts (about 70.4 per cent.), and Coupland about 3,000,000, or 60 per cent. as the mean in seven cases. As concerns the size and shape of the corpuscles, there are different statements. As a rule, they vary considerably in size, but the average is below the normal. This is also the opinion of Hayem and Laache, while Malassez considers the average size of the corpuscles to be increased. This discrepancy may be due to the fact that in the more intense forms, those approaching pernicious anæmia in their symptoms, there is a greater number of large-sized corpuscles. In pernicious anæmia the average size of the corpuscles is decidedly above the normal, and since this fatal affection is due, in my opinion, rather to the prolonged operation of the ordinary causes of anæmia than to one that is specific, it is evident that those cases of chlorosis which approach the border line will show a greater number of large corpuscles than those further removed from it. Chlorosis is to be distinguished from Bright's disease, especially the

insidious form so often associated with contracted kidneys, and from the early stage of phthisis. The former differential diagnosis is to be made by careful, perhaps repeated, examinations of the urine; the latter by means of the thermometer. According to Peter, the surface temperature of the superior intercostal spaces is normal or subnormal in cases of chlorosis, and the same on both sides; whereas, it is elevated on both sides, with a difference between the two, in latent tuberculosis. In chlorosis, also, the phosphates of the urine are below the normal figure, while in early phthisis phosphaturia is quite common. The cardiac murmurs in chlorosis should not be too hastily set down as hæmic. An interesting case in point is reported by Dr. T. K. Chambers ("Renewal of Life")—that of an unmarried servant, æt. 25, with symptoms of anæmia so marked that the attempt to stand upright caused faintness. There was pain in the cardiac region and a loud blowing murmur with the first sound. "This blowing murmur was very audible all over the cardiac region and up the large vessels into the neck, but loudest, and of a harsher character than elsewhere, just at the level of

the aortic valves." Under the use of Mist. Ferri Comp. all the anæmic symptoms disappeared in twenty-one days, although the "cardiac murmur remained as loud, if not louder, and was equally ringing in its tone at the level of the aortic valves." There had been no history of acute rheumatism, and Chambers concluded—and I think most justly—that the cardiac lesion was one of arrest of development.

PROGNOSIS.

The prognosis of recent, uncomplicated chlorosis is good. If of long duration, the nutrition of the cytogenic organs may have suffered to such an extent that they are incapable of resuming their normal functional activity. The case is now inveterate, or pernicious, and its progress is, as a rule, from bad to worse. The blood corpuscles now resemble those of the amphibia in their number, their size, their shape and their percentage of hæmoglobin, and recovery is all but hopeless. Intercurrent febrile and inflammatory affections are more than usually dangerous in cases of chlorosis. The complications to be dreaded in chlorosis are phthisis, gastric ulcer, endocarditis and chorea. There also seems to be a certain causal relationship

between chlorosis and exophthalmic goitre—Graves' disease. The best test of the ultimate prognosis is the immediate effect of proper treatment, the response to which in chlorosis is remarkably prompt and decided.

TREATMENT.

For the treatment of uncomplicated chlorosis, we have a specific in the preparations of iron. To show numerically the effect of this drug, I append the following figures from a case published by me in the Cartwright essay, 1881:—

April 23d,	No. red globules	per	c. mm.,	1,870,000
April 30th,	"	"	"	2,945,000
May 7th,	"	"	"	3,905,000
May 19th,	"	"	"	4,315,000
June 16th,	"	"	"	4,695,000

"This case affords a remarkable instance of the effect of iron in the treatment of certain forms of anæmia. It is classified under the head of chlorosis, on account of the menstrual troubles to which the patient has been subject since the period of puberty, the habitual delicacy of her constitution depending, so far as can be ascertained, upon a chronic deficiency in the blood-making function; and, finally, on account

of the hæmic cardiac murmurs, which gradually disappeared as the quality of the blood improved." The preparations used were, first, the reduced iron, which was afterward changed to the pyrophosphate. Blaud's pill, the protochloride of iron in pill form (Rabuteau's pill), the lactate and the malate, may all be employed. There are many cases in which, owing to digestive troubles, iron cannot be immediately employed. The best method of preparing such patients for specific treatment with iron is a more or less systematic employment of the rest cure, including massage, passive exercise, and a carefully regulated, nutritious diet. Before administering iron, the physician must be satisfied that a cardialgia, if present, is not dependent upon a gastric ulcer. To effect a cure, iron must sometimes be given in heroic doses. Valuable therapeutic data may be obtained by frequent examinations of the blood during the treatment of a case.

ANÆMIA LYMPHATICA.

This disease is almost as rich in synonyms as in symptoms. In addition to the title at the head of this section, the following terms are commonly applied to it: Adenia, Pseudoleu-

kæmia, Malignant Lymphoma, Lymphadenoma, Lymphosarcoma, and Hodgkin's Disease. These are far from being equally appropriate; but something can be urged in favor of each one of these terms, in accordance with the point of view of him who applies it. Thus, the surgeon, having his attention directed to the external manifestations of the disease, will naturally employ one of the titles ending in *oma*, while the countrymen of Hodgkin will continue to make use of the one which associates with the disease the name of the discoverer. I have already written upon this subject, under the title "Hodgkin's Disease," with the explanation that "the perplexing nomenclature of this affection has led the writer to adopt the term 'Hodgkin's Disease,' in the belief that it is more generally understood than any of the other terms employed." From the present standpoint, that of anæmia, it seems to me that the term Anæmia Lymphatica is to be preferred. I refer those who may be interested in investigating the claims of Hodgkin to the discovery of this disease to the *Medico-Chirurgical Transactions*, Vol. XVII, 1832, where it is first clearly described from a clinical point of view.

From a purely anatomical standpoint, Malpighi deserves the honor of having been the first to call attention to the pathological combination of enlargement of the splenic corpuscles which bear his name with general hypertrophy of the lymphatic glands. This is proved by the following quotation, which was brought to the notice of Dr. Hodgkin by Mr. G. O. Heming: "In homine difficilius emergunt (speaking of the granules in the spleen), si tamen ex morbo universum glandularum genus turgeat, manifestiores redduntur, aucta ipsarum magnitudine, ut in defuncta puella observavi, in quâ lien globulis conspicuis racematim dispersis totus scatebat."

The *anatomical features* of anæmia lymphatica are hypertrophy, more or less general, of the lymphatic glands; hypertrophy of the spleen, due to enlargement of its Malpighian bodies; the development of adenoid tissue in various parts of the body; a high, although usually not extreme, degree of anæmia; and the absence of leucocythæmia. It usually begins as a local, glandular swelling upon the surface of the body, which may remain limited for weeks or months to one lymphatic

group. We are ignorant of any law governing the extension of the glandular enlargement. At times it follows the course of the lymph stream ; at others, beginning in the neck, axilla or groin, it will next attack glands in either of these situations on the opposite side. The superficial glands are usually chiefly involved, especially those of the neck and axilla, but cases have been observed in which the morbid process has been limited to the deep lymphatics of the trunk. In a case reported by Osler (*Canada Med. and Surg. Journal*, Feb., 1881) the retro-peritoneal glands were the only ones affected. The enlargement is not inflammatory, neither does it cause inflammation in the surrounding connective tissue. The individual enlarged glands are, therefore, freely movable upon each other, and not united into a dense mass, as in scrofula. Their consistence varies. They may be soft, almost to the point of fluctuation, or of nearly cartilaginous hardness, but no division of the disease can be based upon such differences, for hard and soft glands may be present in the same case at the same time. While the changes characteristic of scrofula —chronic inflammation, suppuration and case-

ation—are conspicuous by their absence, there is no positive antagonism between "lymphadenoma" and scrofula, and, therefore, such changes are now and then encountered. They may be excited by traumatism of the superficial tumors. On section, the soft glands are gray or grayish red, and yield an abundant turbid juice, while the hard ones are, on section, of a yellowish white color, and exude a thin, transparent fluid. Ecchymotic spots and apoplectic extravasations may be present in both forms of tumor. Under the microscope, the difference in consistence of the growths is found to be owing to the degree of thickening of the glandular reticulum and septa. The soft tumors are due solely to numerical increase of the cells, which differ, for the most part, in no respect from normal lymph cells, although, here and there, larger, darkly granular cells, with two or three nuclei, may be met with, and true giant cells, with ten to twenty nuclei. The hard tumors present the same appearances, with more or less thickening of the glandular connective tissue.

The splenic enlargement, although a characteristic feature, is believed to be generally

secondary to that of the glands, for cases have been observed in which, with general involvement of the latter and secondary formations of adenoid tissue in other organs, the spleen remained normal. The enlargement of the spleen is mainly due to an hypertrophy of those masses of adenoid tissue which so closely resemble the lymphatic glands—the Malpighian corpuscles. The spleen, in this disease, never attains the colossal size it sometimes reaches in leucocythæmia, its long diameter rarely exceeding ten inches. The diameter of the hypertrophied Malpighian corpuscles varies from that of a pin's head to one or two centimetres, and their white or yellowish color, like that of the lymphatic glands, contrasted with the dark red color of the pulp, gives to the cut surface a characteristic variegated appearance. Adhesions of the capsule of the spleen to neighboring organs are commonly met with. The enlarged corpuscles may easily be mistaken for tubercular masses, especially as, under the microscope, they are seen to contain the same elements, namely, small round cells, more or less altered in appearance, and giant cells contained in a reticular tissue. The arrangement

of these constituents, however, is, according to Langhans, different from that of tubercle. In the tubercular nodule the reticulum is in the centre, or in a zone between the periphery and the centre, while in the lymphadenoid nodule the reticulum occupies the periphery, the cells the centre.

The infective nature of Anæmia Lymphatica is shown by the development of adenoid tissue in organs and tissues of which it is not a normal constituent, such as the liver, kidneys, lungs, heart, testicles and digestive tract; less frequently the bones, skin and nerve centres. The metastatic nodules spring from the connective tissue of the organ; in the lungs, from the peribronchial connective tissue; in the liver, from the capsule of Glisson, etc. The supposition that they may arise from the endothelial cells of the lymph spaces has not yet been established. The microscopic structure of the nodules has been most carefully studied in the liver, and their origin proved to be in the interacinous tissue, by the fact that a bile duct usually occupies their centre. Dr. Burdon-Sanderson, having observed a thickening of the walls of the intra-lobular capillaries and a

vacuolated condition of the liver cells, thinks it probable that the growth may originate in the glandular tissue. Instead of nodules, a diffuse leucocytal infiltration of the inter-acinous tissue, as in incipient cirrhosis, is sometimes observed. In the lungs, the nodular deposits have been often mistaken for tubercle. They invade the organ from behind forward, starting from already enlarged lymphatic glands. In the kidney the deposit assumes the form of inter-tubular streaks. On the serous membranes it occurs in the form of flattened patches, which may be half an inch in diameter. Under the influence of this disease the thymus gland may, although almost completely atrophied, resume its original shape and size. The follicles at the base of the tongue, the tonsils and the retro-nasal adenoid tissue ("pharyngeal tonsil"), may be so greatly enlarged as to completely occlude the posterior nares. The thickening of the intestinal walls from new formation of adenoid tissue may be enormous, but it has never been known to cause stricture. In a case reported by Dr. Murchison, the walls of the duodenum were from one to two inches thick, and yet the "intestinal mucous membrane corresponding to the morbid deposit

was not ulcerated, and the calibre of the gut did not appear materially narrowed." Various forms of paralysis may be due to the deposit having its seat in the nerve centres, but such cases are exceedingly rare. The blood is diminished in quantity and of poor quality. Macroscopically, it is light colored, thin and uncoagulated in the heart chambers, or, if coagula are present, they are quite small. Careful counts of the blood corpuscles have proved that the diminution in their number is, as a rule, by no means so great as that observed in cases of pernicious anæmia. In four cases carefully studied by Laache the greatest reduction in the number of the red corpuscles was 1,830,000 per cubic millimetre, the count having been made eleven days before the death of the patient. In a case of my own, a boy of five, with enormous enlargement of the right cervical glands, the number of corpuscles per cubic millimetre was 5,462,000, while the hæmoglobin was only sixty per cent. of the normal; so that the functional value of the corpuscles was diminished by forty per cent. In a case reported by Dr. Richard Geigel (*Deutsches Archiv für Klinische Medicin*, Bd. 37, p. 59, 1885), that of a boy twelve

years old, the right side of whose neck was occupied by a glandular tumor as large as a child's head, almost daily counts of the blood corpuscles were made from June 7th to July 23d. The lowest count was 960,000, on July 12th. The percentage of hæmoglobin was never estimated.

Effusion into the pleural and abdominal cavities is often found, and may be due to the irritation caused by growths of adenoid tissue upon these membranes, or to the pressure of enlarged glands upon the vena azygos and the vena portæ. Hydrops lactea may be caused by the pressure of enlarged glands upon the thoracic duct. The bone marrow is very rarely affected. Birch-Hirschfeld knew of but one case in which this tissue was abnormal. The bones themselves, especially the vertebræ, sternum and ribs, may be eroded by the pressure of enlarged glands.

Nature of the Disease.—This is best understood by comparing it with another disease, with which, but for an examination of the blood, it would certainly be confounded, namely, leucocythæmia. Langhans, in view of the fact that the principal distinction between these two diseases is the absence in the former

of an increase in the number of white corpuscles, has suggested their classification under one head, such as adenia or lymphadenoma, with the division into a leukæmic and a non-leukæmic form. Dr. H. C. Wood is of the opinion that, "clinically, the so-called true and false leukæmia are the same, save only in the matter of the white blood corpuscles." This is also the view of Dr. Wm. Pepper, who includes under the term "*anæmatosis*" the affections which I have grouped under the head of primary anæmia, with the exception of chlorosis. The term is apt, convenient and comprehensive, but has not been widely adopted. While admitting the fundamental relationship between these various forms of anæmia, I think that better scientific work will be accomplished by continuing to treat them as separate affections, by dwelling upon their points of divergence. In fact, the tendency of late has been rather to separate than to unite anæmia lymphatica and leucocythæmia. Dr. Moxon and others hold that there is no such disease as pure lymphatic leucocythæmia, the grounds for which will be stated in treating of leucocythæmia.

The disease may be defined as an infective hyperplasia of the lymphatic tissue of the body, with progressive anæmia.

Symptoms.—These are due to the pressure of enlarged glands and new formations of adenoid tissue in the most various situations, causing stenosis of ducts, blood vessels, air passages, œsophagus, etc.; and to the profound disturbance of nutrition and resulting anæmia, which set in sooner or later. By the pressure of the enlarged cervical and bronchial glands may be caused cough, dyspnœa and difficult deglutition, which may all be aggravated by the simultaneous enlargement of the tonsils and retronasal adenoid tissue. The cerebral circulation may also be disturbed by pressure upon the cervical veins. In the axilla, enlarged glands may cause brachial neuralgia and œdema, and enlarged inguinal glands may give rise to similar disturbances in the lower extremity. Enlarged portal glands may give rise to ascites and jaundice. Sensory and motor paralysis may be caused by growths in the brain and spinal cord. Digestive disturbances may be due to the growth of adenoid tissue in various portions of the alimentary canal. As a

rule, the glandular enlargement does not cause pain and is not tender, or very slightly so, on pressure. The same is true with regard to the spleen, but occasionally the hypertrophy of this organ gives rise to a sense of weight and dragging in the left hypochondrium, or even pain that may radiate to the back and opposite side. Pyrexia is frequent during the course of the disease, but presents nothing characteristic, being sometimes continuous, at others remittent or irregularly intermittent. Murchison and De Renzi have each observed a case in which the glandular enlargement, instead of gradually increasing, was paroxysmal, coinciding with attacks of pyrexia of several days' duration. After each attack the enlargement subsided, but remained greater than before. On the other hand, Laache has reported a case in which during the febrile attacks the glands diminished in size. He suggests, in explanation, that a pyrogenic material may be absorbed from the glands. In the great majority of cases no change in the dimensions of the enlarged glands is observed during the attacks of fever. The remaining symptoms are those of steadily progressive anæmia, namely, muscular weak-

ness, paleness of skin and visible mucous membranes, palpitation of the heart with sometimes a systolic murmur, frequent pulse, epistaxis, œdema, and serous effusion not accounted for by mechanical obstruction.

Diagnosis.—This presents certain difficulties when the enlargement remains for a long time limited to one glandular group. It is to be distinguished from scrofula, sarcoma and carcinoma. Strumous glandular enlargement is generally associated with other signs of scrofula, such as affections of the bones, joints, skin and mucous membranes, and especially with the characteristic *facies* of the strumous diathesis. The glands, too, are usually adherent to each other and to the skin, and the morbid process slowly advances to an unhealthy suppuration. In sarcoma, also, the glands are adherent, whereas the tumor of anæmia lymphatica is distinguished by the free mobility of the enlarged glands upon each other. This communicates an unmistakable sensation on palpation, which Southey has aptly compared to that experienced in handling a number of balls enclosed in a net. Carcinoma is almost always secondary, and extends by glandular contiguity, while, as

already remarked, there appears to be no law governing the direction of the progress of lymphadenoma. Leucocythæmia is excluded by a microscopic examination of the blood.

Prognosis.—The prognosis of this disease is not so hopeless as might be inferred from the term, "malignant lymphoma," applied to it by Billroth. In estimating the probable course of a case, and its duration, the most important factor is the stage which the growth has reached. If local, a cure is not only possible, but highly probable, provided the tumor is situated in one of the superficial lymphatic groups; that is to say, within the province of surgery. If the affection has become general, the prognosis is unfavorable; but even then, individual cases present wide differences with regard to the rapidity of their downward course, depending chiefly upon the amount of pyrexia and the degree of anæmia. The average duration of the disease is about two years, but is largely influenced by the preceding health of the patient, being shortest in those of delicate constitution. It has been observed to run a very rapid course after parturition, especially when this had been accompanied with considerable hemorrhage.

Treatment.—An early diagnosis is the most important requisite to a successful treatment. In most of the cases on record the affection has remained limited to one of the superficial lymphatic groups for a varying period, during which the propriety of extirpating the tumor should be considered. By this means the disease may sometimes be cured and its progress often delayed. The enlarged glands must sometimes be removed as a palliative measure, when they threaten to destroy life by impeding respiration or deglutition, or cause intense pain by pressure upon nerves. Friction over the enlarged glands has been said to cause a reduction of their size, and the same result has been attributed to the application of electricity. The general nutrition of the body should be maintained, as far as possible, by a diet as generous as the digestive system can dispose of. The anæmia should be combated with iron and arsenic, and the latter is believed to exert a specific action when injected into the morbid growths. Warfwinge reports several cases cured by the intra-splenic and intra-glandular injection of Fowler's solution. He injected four drops of the solution thrice daily, and observed

a steady reduction of the size of the tumors and a gradual improvement of the condition of the blood.

LEUCOCYTHÆMIA.

The consideration of this disease naturally follows that of the one which has so often been mistaken for it. From the point of view that the genuine should always have precedence over the spurious, it might well have come first in order, but the object of this work, as its name implies, is to keep prominently in view the anæmia common to the various disorders of which it treats. From this standpoint, the anæmia of pseudo-leukæmia, being uncomplicated, deserves the precedence.

Nomenclature.—Of the two names of this disease, leucocythæmia (white-cell blood) and leukæmia (white blood), the former is certainly the more accurate; for the latter might be applied, with equal propriety, to the appearance of the blood after a meal containing an abundance of fat, and in many cases the blood presents to the unaided eye no deviation from the normal appearance. Nevertheless, the term leucocythæmia has been practically rejected by German writers, whose important contributions to our

knowledge of this disease entitle their preferences—or prejudices—to respectful consideration. I shall, therefore, employ both terms interchangeably in the course of this article, giving the preference, when an adjective is needed, to that derived from the shorter of the two.

Anatomical Characters.—This disease is preeminently one to which the term organic or structural may be applied; for it cannot be said to exist until a striking change in the composition of the blood has become manifest. The degree of this change—the increase in the number of the white cells—necessary to constitute the disease, is not agreed upon; and this is not surprising, since, as all are aware, the number of these bodies in healthy blood can only be approximately stated. In health, after meals, the number of leucocytes in the blood is increased, and this increase coincides with a congestion and tumefaction of the spleen, of which the elastic capsule is specially adapted to these periodic changes of volume. This condition of physiological increase in the number of the white cells is known as *leucocytosis*, and the same term is applied to the undue proportion of

these bodies sometimes observed in fevers and during pregnancy. A narrow boundary line between leucocytosis and leucocythæmia cannot be drawn. They are, rather, separated by a broad strip of territory, which either may invade. During the progress of a case of leucocythæmia that may eventually end in death, there may be periods of remission, during which the proportion of white cells to red may be but little removed from the normal; and, on the other hand, a state of the blood at first regarded as a mere leucocytosis may gradually, by its persistence and further progress, convince the observer that he has to deal with a genuine leucocythæmia. The tendency, however, is, rather, to regard leucocytosis as leucocythæmia than the reverse.

Three forms of leucocythæmia are described —the splenic, lymphatic and medullary, which are secondary to changes in those organs—the spleen, lymph glands and bone marrow, universally accepted as *hæmatopoietic*, or blood making. Cases have been supposed to be due to lesions of other organs, such as the thymus and thyroid bodies, the tonsils and intestinal glands, but these were mostly reported before

Neumann had directed attention to the marrow as a *fons et origo mali*, and there is no proof that such cases were not of the medullary or myelogenous form. As the affection is mostly one of adult life—the greatest number of cases occurring between thirty and fifty years of age—the part taken in its production by a fœtal organ, such as the thymus, is highly problematical.

The first stage of the morbid process in the spleen is a hyperæmia, which may be so intense in degree and so rapid in development, as to cause great enlargement of the organ and sensations of discomfort, weight, and even pain, in the left hypochondrium. The tissue of the gland is soft and its surface irregular, the depressions corresponding to the insertions of the fibrous trabeculæ. At this period the condition differs only in its degree and persistence from that which normally exists during digestion. Soon, however, the enlargement acquires a more permanent—a structural—foundation, from numerical hypertrophy of the cells of the splenic pulp. The size of the organ increases, and may become so enormous as to fill the space between the ribs and groin on the left side, and extend

beyond the umbilicus on the right. The results of inflammation of the capsule are commonly apparent in the form of thickenings, opacities and adhesions to neighboring organs. The gross appearance of the cut surface is variable. Sometimes it differs in no respect from that of a normal spleen; at others, all traces of the Malpighian bodies have disappeared; the section is smooth and firm, closely resembling that of the liver. In the pure splenic form of leucocythæmia the Malpighian bodies, while, perhaps, plainly evident, are not enlarged. They become so only in the lymphatic and lieno-lymphatic forms. Hemorrhagic infarctions are often observed.

The alterations of the lymphatic glands, like those of the spleen, are due to simple hyperplasia, and have been already described in the section on anæmia lymphatica. In leucocythæmia their consistence is usually soft.

The changes in the bone marrow, to which attention was first called by Neumann, are twofold. In the first form it is of grayish-yellow or yellowish-green color, and closely resembles a thick, creamy pus; in the second, more or less of

red is mingled with the gray or yellow, until in the most marked degrees of this variety the medulla may be of the color of raw beef. These variations in color are explained by Ponfick as being due to varying densities in the accumulations of white cells and corresponding variations in the amount of blood in the vessels. The leucocytes are seen, under the microscope, to be embedded in an extremely fine reticular tissue. In this altered marrow there may be apoplectic extravasations such as have been described as occurring in the spleen and lymph glands. The bones, of which the medulla most frequently undergoes these changes, are the sternum, ribs and vertebræ.

In other than lymphatic organs, any alterations are due to the altered state of the blood, and consist of the fatty degenerations common to anæmia in general and of infiltrations and nodular deposits of leucocytes. The infiltrations are most common in the liver and kidneys, causing considerable enlargement of these organs. The nodules have been observed both in the substance of organs and on their serous surfaces, as well as on the mucous membranes of the air passages and stomach. The peri-

toneum may be covered with gray, semi-transparent nodules varying in size from a pin's head to a pea, and so closely resembling miliary tubercle in their gross and microscopic appearances that the absence of the bacillus may be the only differential point. The minute structure of the nodules of this "leukæmic peritonitis" may also resemble that of alveolar sarcoma, as in a case described by Laache.

Changes in the Retina.—In well-marked cases of leucocythæmia, certain retinal lesions are commonly observed, to which attention was first directed by R. Liebreich in 1861. Being generally situated near the periphery of the fundus oculi, they but seldom cause any visual disturbance, and, therefore, their frequency can only be estimated by an ophthalmoscopic examination of all cases. The eye-ground is of an orange-yellow hue, its veins pale and wider than normal, and traces of hemorrhage are scattered along their course. Other spots are observed, of which the appearance indicates a more compound structure than that of mere hemorrhage. They have a whitish-yellow centre and a reddish border of extravasated blood, and are analogous to the lymphoid deposits

in other tissues. The cause of these retinal hemorrhages is twofold. They are favored by the malnutrition of the vessels from deficiency of red corpuscles, and excited by the obstructions from excess of the white.

Changes in the Blood.—The characteristic feature of leucocythæmia is an absolute increase in the number of white blood cells, which in extreme degrees of the disease may be even greater than that of the red. This alteration in the cellular composition of the blood may alter its macroscopic appearance by causing it to assume a pale-red, grayish-red, or chocolate color ("milchchocolade"); but it would be exceedingly rash to predict the existence of leucocythæmia from a gross examination of a specimen of blood. Such a caution will not seem unnecessary to those who, like myself, have seen a case reported as leucocythæmia in which the blood was never examined at all. The white cells are by no means uniform in size. In one of Mosler's cases the smallest were one-third smaller than the red; the largest four times larger than the red. It is doubtful whether, as Virchow supposed, any diagnostic significance can be attached to such

variations; for in a case of pure splenic leucocythæmia the leucocytes have varied in diameter from 5 μ to 15 μ. Virchow holds that in the latter variety the leucocytes in the blood are identical with the cells of the splenic pulp, and that in the lymphatic form they are uninucleated like the cells of the lymphatic glands. Before attempting, however, to make the diagnosis of a disease, it is necessary to establish its existence, and that of the so-called lymphatic leucocythæmia is emphatically called in question. In the medullary form, Neumann has found in the blood, red nucleated cells such as normally inhabit the marrow, and regards them as characteristic of this variety. They are not always present, having been searched for in vain by Mosler in a typical case of medullary leukæmia (*Berl. klin. Woch.*, 1876, No. 49).

The degree of anæmia is rarely extreme. ases may steadily proceed to a fatal termination without a reduction of more than fifty per cent. of the normal number of red corpuscles, although exceptional cases occur in which the number of red corpuscles is exceedingly small; for example ,0.5 million per cubic millimetre. There are no characteristic changes in the size

and shape of the red corpuscles. The value of the latter (their percentage of hæmoglobin) is well maintained, rarely sinking below seventy-five per cent. A point of some importance with reference to the pathogeny of the disease is that the number of white and red cells together is less than that of the normal number of red. Certain pointed octahedral crystals were discovered in leucocythæmic blood by Charcot in 1853, identical with those subsequently observed by Leyden, in 1871, in the sputa of asthmatics. In 1860, in a case reported by Dr. Calvin Ellis, Dr. White found "numerous minute crystals. They were colorless, elongated, faintly marked, rhombic octahedra, exhibiting irregularities of form, indicating an organic nature." To these crystals he gave the name of "*Leukosin*." In 1863 Dr. Howard Damon discovered, in the leucocythæmic blood of a boy, certain crystals which, he asserts, "differed entirely, in form, size, color, degree of resistance at atmospheric influences, refractive and other properties, from all known crystals of the human blood." They were composed of "hexagonal and pentagonal plates of unequal sides, of rectangular plates in the form of squares and

parallelograms, and also of a few triangular plates. Some of these crystals were twice the size of the red blood corpuscles in the same field of view." The name of "*Leucocrystallin*" was applied to them by Dr. Damon.* Certain normal constituents of the spleen have been found in leucocythæmic blood, such as lactic and formic acids, leucine and hypoxanthine. The specific gravity of the blood is diminished in leucocythæmia owing to the fact that the red corpuscles are replaced by the lighter leucocytes; and, further, because the normal proportion of water is retained. The proportion of fibrin is, as a rule, increased.

Clinical History.—In the insidious nature of its onset, and its gradual progress, leucocythæmia resembles many fatal diseases which run a chronic course. The first symptoms complained of are those of anæmia in general, such as muscular weakness, lassitude, indisposition to exertion, either physical or mental, anorexia, indigestion, and dyspnœa, on exertion. As the case progresses, other symptoms arise, of which some are to be attributed to leukæmic deposit in

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* See Bolyston Prize Essay on Leucocythæmia, 1864.

the parts affected. Among these are hemorrhages, either spontaneous or traumatic; the former variety being most commonly met with in the form of epistaxis; the latter, after the extraction of teeth. Diarrhœa is now the rule, and œdema of feet and legs and ascites finally set in. The last-named symptoms are most common when the spleen is greatly enlarged and indurated, and are favored by deposits in the liver and by the leukæmic peritonitis above mentioned. Singular anomalies are sometimes observed in the course of this disease. For example, although the appetite is generally markedly deficient, often to the point of absolute anorexia, it may be voracious, as in a case observed by Prof. Da Costa (*Am. Jour. Med. Sci.*, Jan. 1875), in which, in spite of an inordinate consumption of food and the absence of diarrhœa, the loss of flesh was progressive. On the other hand, in a case reported by Mosler, in which the blood was chocolate-colored and the white cells were to the red as two to three, the digestion was unimpaired and the body weight maintained. Dizziness, aggravated by movement, may be a marked symptom. In the splenic form, sensations of weight, dragging

and pain are felt in the left hypochondrium ; and in the medullary variety, tenderness of bones, particularly the sternum, may be detected. Visual disturbances may be due to hemorrhage, to leukæmic deposit, or to leukæmic retinitis ; but marked retinal changes may be observed in cases which have presented no symptoms of eye disease. There is no peculiar facies of this disease. The extreme pallor of pernicious anæmia is rarely observed. On the contrary, the cheeks often present a circumscribed flush, even in a late stage of the affection. There is nothing typical in either pulse or respiration, but fever of irregular type is invariably met with at some period of the clinical history. The proportion of white cells to red is diminished by the occurrence of suppuration in any part of the body. When the leukæmic cachexia is fairly established, the enlarged spleen may diminish greatly in size without any corresponding improvement in the symptoms. In a case reported by Laache, the spleen, which had projected to the right, beyond the median line and downward almost to the symphysis pubis, gradually contracted until, just before death, it extended but three centimetres below the left costal border.

Hypoxanthine is found in the urine as well as in the blood, and in the former fluid the proportion of uric acid is increased, sometimes to six or eight times the normal.

A division of the course of the disease into two stages has been suggested: the first consisting of the development of the morbid process in the hæmatopoietic organ or organs first attacked and in the blood; the second, of the extension of the process to other non-lymphatic organs. This division, although excellent from an anatomical standpoint, is too objective for clinical purposes. The secondary leukæmic deposits cannot be detected, as a rule, in any organs but the lymph glands, assuming, for the moment, that the enlargement of these organs is secondary.

Pathogenesis.—To properly appreciate the cause of any deviation from the normal composition of the blood, it is necessary to understand how that composition is produced and maintained. In the problem before us—the nature of leucocythæmia—the first step is to decide whether there is any normal relationship between the red and white cells. If there be any, it is manifest that the red, on account of their greater functional importance, their size,

shape, color and number, are derived from the white, and not the white from the red. The question, therefore, is one concerning the origin of the red corpuscles; and those who have studied it will doubtless agree with me that there is scarcely a subject in physiology concerning which our notions are so fragmentary and confused. This being the case, it is impossible to offer more than an hypothesis of the nature of leucocythæmia.

All authorities are agreed that in adult life the lymphatic system—in which are included the spleen, lymphatic glands, and red marrow—is the sole source of the red blood corpuscles. The cells of the splenic pulp, the smaller uninuclear cells of the lymphatic ganglia, and the red, nucleated marrow-cells—first described by Prof. Neumann, of Königsberg, in 1868, and subsequently called by Malassez, "*cellules hémoglobiques*"—are by some, perhaps different, means converted into the bi-concave discs of the circulating blood. Time is requisite for this conversion—a time of incubation in the blood-making organs. Any unusual activity of the circulation in these glands may hasten the exit of their cells, and cause them to appear in the

blood in an immature condition. This is demonstrated by the physiological concurrence of leucocytosis with splenic post-prandial congestion. In leucocythæmia, there is a persistent hyperæmia of spleen or other blood-making organ, which prevents the leucocytes from attaining their proper development. They enter the circulation as leucocytes. This view is endorsed by Dr. Richard Norris, of Birmingham, and held by others, who do not agree with him concerning the stages of the process by which the white cells are normally elaborated into red corpuscles. Norris contends that in health the great majority of the leucocytes in the blood-making organs are, before entering the circulation, converted into a pale, colorless, biconcave disc, which he terms the "advanced lymph disc." This corpuscle acquires hæmoglobin, and with it its full functional perfection. The white blood corpuscles represent those leucocytes which have prematurely entered the circulation, for instance after a meal. These latter, however, may develop into red corpuscles in the circulation. The former mode of origin of red corpuscles Norris calls the "major process" of blood-formation; the latter, the

"minor process," and, therefore, in accordance with his views, "leukæmia, in a word, is the encroachment of the minor upon the major process of blood-making."

Several observers have noticed a diminution or absence of amœboid movement in the white cells of leucocythæmic blood. "The earliest observations on this point were made by Dr. Laking, in 1873, but remained unpublished. The results were communicated by Dr. Pye-Smyth to the Pathological Society in 1878, and, in the same year, to the *Lancet*, by Dr. Cafavy. Neumann also, in 1878, found amœboid movements wanting, or very sluggish, in a case of leukæmia, although they were active in the corpuscles of fluid from blisters in the same patient." (*Lancet*, 1880, ii, 769.) Dr. John Cafavy, who has given special attention to this subject, concludes that "the colorless corpuscles in leukæmia are dead, or dying, and hence incapable of development." This functional incapacity of the white cells may be referred to the shortness of their stay in the lymphatic organs, of which the hyperæmia prevents their reaching the normal term of their gestation. They are to be regarded as abortive products.

Under this section it is appropriate to consider the question, which has been raised, as to whether the customary division of this disease into three varieties, the splenic, lymphatic and medullary, is warranted. A primary splenic leucocythæmia being universally accepted, it remains to consider whether the lymphatic glands and the bone marrow may be the starting point of the disease. Some authorities, while not explicitly rejecting the lymphatic and medullary varieties, do so tacitly by describing no other than the splenic. Dr. Moxon is the most outspoken upholder of the doctrine that the spleen is the only starting point of leucocythæmia, and emphatically rejects the theory of a lymphatic leukæmia, which he stigmatizes as a "myth." He holds that the enormous accumulations of leucocytes in the lymph glands and bone marrow are secondary deposits from the blood, and, in support of this view, he has demonstrated that the leucocytes normally present in the lymph spaces—which have been shown by Dr. Klein to be out-wandered white blood cells—are greatly increased in number in cases of leucocythæmia. These cells are conducted through the lymphatic

vessels to the glands, and if these are pervious, re-enter the blood; if not, the glands enlarge by the continual accession of out-wandered blood cells; "so that," Dr. Moxon concludes, "lymphatic leukæmia is a myth; and the pathology of leukæmia, now so complex, should be simplified, when it will better conform with the clinical uniformity which characterizes the disease." I am inclined to accept Dr. Moxon's opinion in so far as the lymphatic variety is concerned, for the reason that in anæmia lymphatica we find a lesion of the glands identical with that which exists in lymphatic leukæmia. The last-named affection, assuming its existence for the sake of the argument, is made up of lymphatic anæmia plus leucocythæmia. I believe, however, that there is substantial proof of the existence of a primary medullary leukæmia. For example, in a case observed by Virchow, fracture of the femur appeared to be the determining cause. In another, reported by Mursick, the disease attacked a soldier five days after amputation for a gunshot wound of the knee-joint, and at the autopsy osteo-myelitis of the femur was found. The patient had been previously healthy. In the remarkable case of a

sea captain, reported by Mosler, in whom the disease followed prolonged exposure to cold during an Arctic winter, pain and tenderness over the entire length of the sternum were among the earliest symptoms, and speedily became so intense as to compel the man to desist from any kind of manual work. The list of cases such as those last referred to is so long, and the cases themselves so remarkable, that those who are at all familiar with them feel the necessity of great caution in discussing the question of a primary medullary leukæmia. As above stated, I believe the evidence is in favor of such an affection, and, with the object of obtaining further confirmation, I would suggest to hospital surgeons and their assistants the importance of examining the blood after injuries of the bones.

Ætiology.—The male sex is more predisposed to this disease than the female, the male cases on record standing to the female in the proportion of about two to one. The influence of age is not striking, although the disease occurs most frequently during adult life, and between the ages of thirty and fifty. Neither infancy nor old age is exempt. Cases in infants of

fifteen and sixteen months have been reported by Trousseau and Mosler, and one of Vidal's cases was sixty-nine years old. Dr. Goodhart has also reported to the Clinical Society of London six cases under two years of age. Poverty includes, in one word, a number of predisposing factors, such as an unfavorable hygienic environment, insufficient food, and the depressing emotions of care and anxiety. A few cases have been attributed to traumatism of the spleen, and others, as already stated, to that of the bones. There can, I think, be no doubt that long-continued exposure to severe cold has excited the disease in several instances.

Diagnosis.—This can be made in no other way than by a microscopic examination of the blood, and to warrant the diagnosis of leucocythæmia, the increase in the number of the white cells must be absolute as well as relative. In well-marked cases the microscopic inspection of a drop of blood will suffice for the barest purposes of diagnosis, but will give no idea of the grade of the affection. With the latter object in view, the number of red and white corpuscles in a given volume of blood—a cubic millimetre—must be estimated by means of a

hæmacytometer, such as that of Gowers or Zeiss. I have more than once refuted a diagnosis of leucocythæmia which had been made by the examination of a drop of blood under the microscope. In one of the cases the diagnosis thus made seemed unmistakable, but on carefully counting the red and white cells, I found a great reduction of the former, and a proportion of one to eighty between the white and red, but *the number of the white cells per cubic millimetre* was within normal limits. In every case of profound anæmia in which the number of white cells is not reduced *pari passu* with the red, the diagnosis (?) of leucocythæmia is liable to be made, unless the most accurate methods of investigation are employed. I have seen as many as from twelve to fifteen white cells in each microscopic field of a specimen of blood of which a more careful examination showed that the increase was merely relative. The liability to error being so great, what is the increase, absolute and relative, which warrants the diagnosis of leucocythæmia? There is no fixed rule. Each observer is a law unto himself. For my own part, if the number of leucocytes per cubic millimetre is increased (*i. e.*, if

they are more than 10,000), and if the proportion of white cells to red is as great as one to fifty, I consider that the limits of leucocytosis have been overstepped. This is confirmed by the co-existence of great tenderness of sternum, ribs or vertebræ, and made absolutely certain by the detection of any enlargement of the spleen. As to the question whether the precise variety of the disease may be ascertained by an examination of the blood, there is little to be said. As already mentioned under the head of changes in the blood, the size of the white cells may vary greatly in the purely splenic form. The presence of red nucleated cells in the blood is believed by Neumann to be pathognomonic of the medullary variety, but their absence does not exclude an implication of the marrow. The absent or diminished amœboid movement of the white cells is a point with which diagnosis is not so much concerned as pathogenesis, and, therefore, it has been referred to under the latter head.

Dr. Richard Geigel (*loc. cit.*) has suggested and practiced the following method for making easier the counting of the white cells. To fifty cubic centimetres of a one-half of one per cent.

chloride of sodium solution, are added four drops of a one and one-half per cent. solution of gentian violet, and by using this in the counting of the corpuscles, instead of the ordinary diluting fluid, the red corpuscles are unaltered, while the leucocytes are stained blue, so that it is impossible to overlook a single one of them.

The diagnosis of leucocythæmia having been made with the microscope, its variety is to be determined by the ordinary methods of physical diagnosis. A case in which the spleen is increased in size, while nothing abnormal can be detected in lymph glands or bones, is one of pure splenic leukæmia. Combinations of enlarged spleen and lymph glands are designated as lieno-lymphatic or lymphatico-splenic, in accordance with the supposed priority of the organ affected. The medullary form may also be complicated with an enlarged spleen or with hypertrophied lymphatic ganglia, and the same remarks are applicable to it.

Prognosis.—In the earliest stage, that of hyperæmia of the hæmatopoietic organ involved, a cure may be effected by a proper course of treatment. The prognosis is more unfavorable

when the enlargement of spleen or other organ is maintained by numerical hypertrophy of its cells, and becomes absolutely so when the leukæmic infection has become general. The latter event—the establishment of the leukæmic cachexia—may sometimes be demonstrated by an inspection of the fundus oculi, in which leukæmic deposits are readily seen. A not uncommon mode of death is apoplexy, to which there is a predisposing cause from malnutrition of vessel walls, and an exciting one from accumulation of leucocytes within their lumina.

From one to three years is the average duration of the disease.

Treatment.—The cures reported have been mostly in children, which may be owing to the fact that their impressible systems render easier an early diagnosis. The very fact that their powers of resistance are less than those of adults is thus favorable, from a therapeutic standpoint. Dr. Goodhart has reported to the Clinical Society of London six cases of children, under two years of age, which were cured by the administration of either phosphorus, iodide of iron, or cod-liver oil. In all of them the spleen was moderately enlarged and the white

cells increased about tenfold. Mosler also has reported the cure of a boy of ten years, who "took a drachm and a half of sulphate of quinine in the course of four days, and then ten grains, and afterward six grains daily; he completely recovered." The case was of the splenic form. Mosler prefers quinine to all internal remedies, but recommends also the employment of oil of eucalyptus and piperin, in accordance with the results of certain experiments by himself and Hans Sœnderop, which show that both these substances cause contraction of the spleen in dogs. They may be prescribed in pill, as in the following formula:—

℞.	Ol. eucalypti,		gtt. 100
	Piperini,		
	Ceræ albæ,	āā	ʒj
	Pulv. altheæ,		ʒij.

M. et ft. pil. No. C.

Sig.—Three to five pills thrice daily.

Careful counts of the blood corpuscles during the employment of arsenic, have proved that this drug has a favorable influence over the course of leucocythæmia. It should be given in full doses and pushed to the point of toleration. A local treatment of the enlarged spleen by

means of electricity, cold douches, and ice bags, has been practiced, and often with the result of materially reducing its size. Once, however, the disease is fairly established, the spleen may fluctuate very greatly in size, without any corresponding effect upon the patient's condition. In the early stage of the splenic form, local treatment should not be neglected. Botkin reports a case of lieno-lymphatic leukæmia in which faradization was followed by a considerable reduction in the long and transverse diameters of the enlarged spleen, which coincided with improvement in the general condition of the patient. In opposition it must be stated that Mosler has not been able to confirm the statement that the size of the spleen is reduced by faradization, but has seen its long diameter *apparently* diminished by being pushed upward by the contraction of the abdominal muscles. Transfusion of defibrinated blood has been employed with marked temporary benefit, but cannot be regarded as a curative measure.

Extirpation of the spleen is only mentioned for the purpose of condemning it.

Postscript.—Although not without an opinion

concerning the rival claims of Bennett and Virchow to the discovery of leucocythæmia, I have, thus far, purposely refrained from expressing it. It appears to me that the credit of having presented the subject of leucocythæmia in such a light as to attract the notice of the whole profession, and to convince Bennett that six weeks before he had *discovered* a new disease, undoubtedly belongs to Virchow. I also think that when a labored argument, such as that of Bennett, is necessary to make good a claim, it is self-evident that the right of possession can be called in question.

ANÆMIA SPLENICA.

Definition.—This disease, which is *the splenic form of pseudoleukæmia*, is completely ignored by nearly all the numerous text books, hand books, systems and cyclopædias of medicine. Even Dr. Adolph Strümpell, who published an elaborate article in the *Archiv der Heilkunde*, Vol. XVIII, 1877, entitled *Zur Kentniss der Anæmia Splenica*, devotes but eight lines to this subject in his recent text book of medicine. Although apparently unknown to most of the writers of the works above mentioned, splenic

anæmia has long been recognized as a distinct affection by those who have paid special attention to diseases of the hæmatopoietic organs. For example, in the course of an article on the "Relations of Leucocythæmia and Pseudoleukæmia," in the *American Journal of the Medical Sciences* for October, 1871, Prof. Horatio C. Wood remarks: "I now desire to show that there is still a third form of pseudoleukæmia—a splenic variety. Under the names of tumor of the spleen, splenic cachexia, etc., from time far back, medical records furnish accounts of cases which I believe represent this affection." He then proceeds to report a typical case of anæmia splenica.

The best account of this affection that I have been able to find in medical literature is by Dr. Guido Banti (*Annali Universali di Medicina Chirurgia-Parte Rivista*, 1883), and is based upon a critical study of three cases: a woman of 73, a boy of 18, and a girl of 16. To it, as well as to the article by Strümpell above referred to, I am largely indebted for the following description.

Anatomical Characters.—The cadaver presents the well-known appearances of extreme

anæmia, and there is usually a certain amount of subcutaneous œdema and serous effusion. The spleen, while retaining its shape, is enlarged, sometimes to thrice its normal size; its tissue is more or less indurated, and its incisures deeper than normal. The capsule presents patches of thickening and opacity, and is sometimes adherent to neighboring organs. On the surface of a section which is of a reddish-brown color, white or yellow-white spots, usually not exceeding the size of a pea, may often be observed. With the microscope, it is found that the normal adenoid tissue has more or less completely disappeared, its place being more than supplied by a thickening of the reticulum, which, in parts of the organ, may be so great as to form parallel bundles of fibrous tissue, containing narrow lacunæ, in which are embedded a few lymphatic cells. The change is precisely similar to that of the indurated glands in anæmia lymphatica, and in order to emphasize the fibrous character of the alteration in both these diseases, Banti proposes for it the name of *fibroadenia*. In the heart and voluntary muscles, fatty changes are the rule. The blood corpuscles are notably diminished. From

5,000,000 per cubic millimetre, they gradually descend to four, three, or even one million. In a case of my own their number was between one and two millions. They present the same alterations in size and shape as are encountered in all pernicious forms of anæmia. Notwithstanding Banti's assertion that red nucleated cells have never been observed in the blood of splenic anæmia, they are said, by Strümpell, to have been numerous, in his case, in blood from the veins of the lungs, liver and spleen. They varied greatly in size and shape, and were mostly uninuclear, although some contained two nuclei, and a few contained three. With reference to the proportion of white cells, the cases may be divided into two classes. In the first, the normal number of white cells is not surpassed. In the second, the white cells are increased in number, without, however, exceeding the limits of leucocytosis. Their protoplasm is granular, and, on the addition of acetic acid, becomes transparent, and shows, as a rule, but one nucleus. They do not contain pigment granules, and, on a warm stage, exhibit well-marked amœboid movements.

The marrow may present the changes that

have been erroneously supposed to be peculiar to the so-called progressive pernicious anæmia. In Strümpell's case the medulla of sternum, ribs, and tibiæ, was of a dark-red color, and of unusually firm consistence, and presented the following minute changes: 1. Scarcely any fat cells were present. 2. The colorless marrow cells were of widely different size and shape, mostly uninuclear, though some contained two nuclei and others enclosed red blood corpuscles. 3. Besides the ordinary red blood corpuscles, there were numerous round, pale-red, non-nucleated cells of different size, and many red nucleated cells of varying size and shape, some round, others elliptic; the former sometimes granular, the latter mostly homogeneous. Their nuclei were often double, and of the same pale-red color as the rest of the cell; sometimes of a more yellowish tinge. Occasionally, the nucleus was enlarged so as to almost fill the entire cell; often it was placed eccentrically.

Clinical History.—The disease may be properly divided into three stages, of which the first, the enlargement of the spleen, is often so insidious as to pass for a long time unobserved by both patient and physician. It mani-

fests itself more frequently by a sense of weight in the left hypochondrium, which may be experienced only when in the upright position. Sometimes, however, it gives rise to severe neuralgic paroxysms. The second stage, that of anæmia, presents the phenomena of anæmia in general, such as pallor of skin and mucous membranes, dyspnœa, cardiac palpitation and fatigue, on slight exertion. These symptoms increase in severity until the third stage, that of cachexia, is reached. The distinguishing features of this stage are hemorrhage and fever. The skin is now the color of yellow wax; the muscular prostration is extreme; the mental state is one of hebetude, and the œdema and serous effusions increase. The adipose tissue generally disappears to a greater or less extent, but is sometimes preserved. The disease, instead of being continuously progressive, may recur in separate attacks, between each of which there may be intervals of good health, of several months' duration. This intermittent character of the affection was particularly well marked in the case reported by Strümpell, that of a young man, æt. 25, who, in the course of eighteen months, was the subject of four attacks of pro-

found anæmia, each of which coincided with enlargement of the spleen. Twice he recovered from an apparently hopeless condition. A third attack ensued after several months of good health, and he was again improving when he fell into a state of melancholia, during which the fourth attack occurred and was fatal.

Careful examinations of the urine were made by Strümpell in the case referred to. It was always acid, never contained albumin and, notwithstanding the icteric hue of the skin, never responded to the tests for bile pigment. Repeated examinations showed that the greatest destruction of albumin in the body, inferred from the amount of nitrogen excreted, coincided with the worst periods of the anæmic attacks. This fact is in perfect analogy with certain physiological experiments of Bauer and Fränkel. The former found, after bleeding animals, that the destruction of albumin in their bodies was augmented. The same was true in cases of phosphorus poisoning, in which there is destruction of red cells. Fränkel demonstrated an increased excretion of urea after any obstacle to respiration had been placed in the large air passages. A similar increase had been demon-

strated in cases of carbonic oxide poisoning. As is well known, in cases of CO poisoning the functional power of the red corpuscles is paralyzed; they cannot carry O until the CO is displaced. In a word, experiments show that any cause which interferes with the conduction of oxygen to the tissues may produce secondarily an increased destruction of albumin in the body; and this is found also in states of profound anæmia in which the diminished consumption of O is inferred with almost absolute certainty from the fact of an enormous destruction of O carriers, and is confirmed by the presence of fatty degeneration of heart, blood vessels, etc.

Nature of the Disease.—Although anæmia splenica has been generally confounded with other forms of pernicious anæmia, there can be no question that it constitutes a distinct pathological entity. The enlargement of the spleen is primary, the anæmia secondary; as to the relation between them, there are two hypotheses —to wit: Either the altered spleen directly destroys the red corpuscles, or in it are formed materials which enter the circulation and interfere with the functions of hæmatopoiesis. Of these views, Banti espouses the latter. With

regard to the primary enlargement of the spleen, nothing is known. That the disease is the splenic form of pseudoleukæmia, is, according to the author just cited, proved by the following facts. In pseudoleukæmia (*i.e.*, anæmia lymphatica, or Hodgkin's disease), the lymphatic glands are rarely the only organs affected; generally the spleen is enlarged at the same time. In some cases, the enlargement of the spleen is in much greater proportion than that of the glands, and, finally, there are cases (and these belong to the category of anæmia splenica) in which the spleen is alone involved.

The view that this disease is the splenic form of pseudoleukæmia may be opposed on the ground that the morbid changes in the spleen in anæmia splenica are not identical with those of the same organ when affected in anæmia lymphatica. In the latter disease, the malpighian bodies of the spleen, when that organ is secondarily affected, are hypertrophied to such an extent that, as I have said under the head of "Anæmia Lymphatica," "their white or yellowish color, like that of the lymphatic glands, contrasted with the dark-red color of the pulp, gives to the cut surface a characteristic variegated

appearance." This change is beautifully shown in a plate illustrating an article on Lymphadenoma by Dr. Murchison, in the *London Path. Soc. Trans.*, vol. XXI. In marked contrast to this description, the spleen, in the case reported by Prof. H. C. Wood, was much enlarged and indurated, but the "*malpighian corpuscles were not at all evident.*" In summing up the anatomical characters of the disease, Banti says, with reference to this point: "The histological alterations of the spleen consist of an *atrophy and sclerosis of the malpighian corpuscles*," etc.

These apparent discrepancies may be explained in this manner: The spleen is not a lymphatic gland, but contains within its pulp numerous bodies—the malpighian corpuscles—analogous to the lymph glands. As the latter may, or may not, be enlarged in cases of pseudoleukæmia—using this term in its broadest sense—so their analogues in the spleen may, *or may not*, be enlarged.

Course and Prognosis.—The duration of splenic anæmia is from five or six months to three years. These figures are certainly within the mark, for in all the cases, owing to the insidious nature of the onset, more or less of

the first stage passes unobserved. The disease sometimes occurs in separate attacks, from all of which, except the last, there may be complete restoration to health; and, on account of this peculiarity in its course, there is great danger of prematurely reporting cases as cured. According to Strümpell, permanent cures are unknown; but this opinion must be modified in favor of a few cases in which splenectomy has been practiced successfully.

Diagnosis.—The tumor being recognized as an enlarged spleen, by its situation, shape and mobility during respiration, the question arises as to the character of the enlargement. There is no difficulty in distinguishing the tumor in anæmia splenica from other tumors of the spleen which alter its normal shape, such as carcinoma and echinococci, but the tumors of amyloid disease, paludal cachexia and leukæmia are to be carefully differentiated. Amyloid disease is secondary to suppuration, especially in or about the bones; to syphilis, or to phthisis, and is not confined to the spleen. It may be demonstrated at the same time in the liver, and perhaps also in the kidney, by an examination of the urine. Leukæmia splenica is excluded by a careful

count of the white and red cells; and paludal cachexia by the history of the case and the presence in the blood of the plasmodium malariæ.

A case of anæmia of high grade associated with a uniform splenic enlargement, not malarial, leukæmic, or amyloid, can be no other than one of anæmia splenica.

Treatment.—The medical means of relief are the same as those employed in other pernicious forms of anæmia, and have been, thus far, attended with but little success. Among them are the salts of quinia, piperin, oil of eucalyptus, and arsenic. The latter may be given by the mouth, or may be injected into the splenic pulp, as has been done with marked success by Warfwinge, in cases of anæmia lymphatica.

Faradization should be given a thorough trial; for, even admitting that it has no direct effect upon the spleen, there is reason to believe that a salutary influence is exercised upon that organ by the contraction of the abdominal muscles.

Pain, vomiting, diarrhœa, ascites and epistaxis are to be treated in the same manner as in other diseases attended with these symptoms. Banti

has tabulated the cases of splenectomy performed for non-traumatic lesions. They number twenty-one, of which four were undoubted cases of anæmia splenica. Of these four, three recovered.

PERNICIOUS ANÆMIA.

Nomenclature.—The term idiopathic was first applied by Addison to certain cases of profound anæmia of unknown origin, which were in all respects identical with those subsequently described by Biermer, in 1872, under the title of "progressive pernicious anæmia." In the latter term the adjective "progressive" appears to me not only unnecessary but, to a certain extent, absurd; for all diseases are progressive in one or other direction. In using the term "idiopathic," Addison was, no doubt, impressed with the idea that when the anatomical basis of a disease is unknown, it is best to apply to it a title acknowledging that ignorance. This I regard as an error. It is one thing to acknowledge ignorance and another to parade it. A terminology based upon etiology is doubtless the most scientific, but one based upon symptomatology is not unscientific. I fully agree with the late Dr. Fagge that the "phenomena

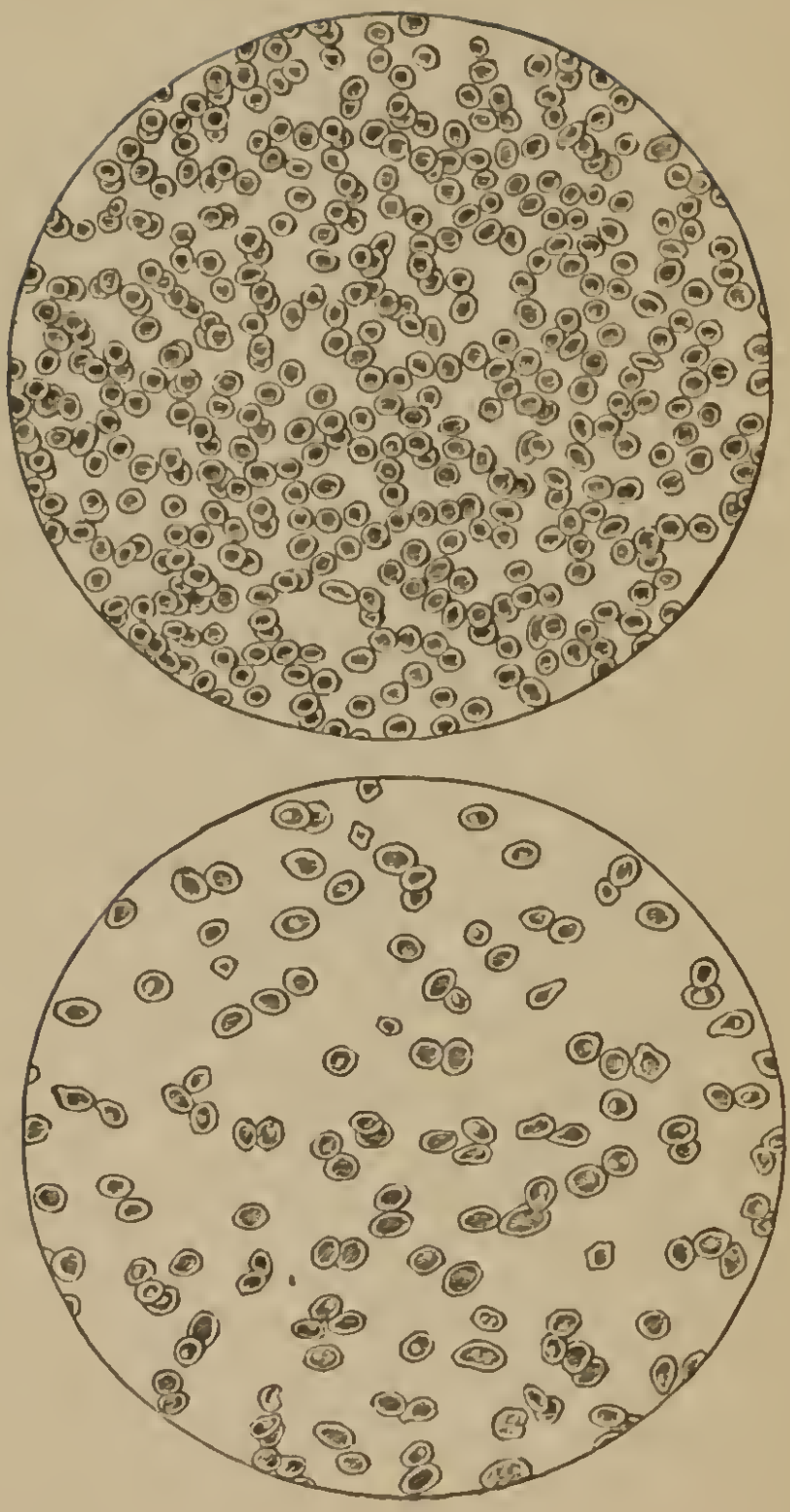
which are commonly spoken of as symptoms are part of the disease to which they belong, no less than the lesion or the specific cause or whatever is taken as its main characteristic." To those who may think these remarks unnecessary, it is a sufficient reply that our knowledge of the causes of several forms of miscalled idiopathic anæmia dates from the time when Biermer substituted a significant symptomatic term for one that had nothing but vagueness to recommend it.

Nature of Pernicious Anæmia.—In placing pernicious anæmia in the category of primary anæmias, although I do not regard it as an independent disease, I have not been inconsistent. An anæmia becomes pernicious when the blood corpuscles undergo a series of changes which cause them to resemble, in more than one respect, the corpuscles of the amphibia. Pernicious anæmia is the final stage of several forms of symptomatic anæmia and of chlorosis. The prognosis of anæmia *per se* is good until the changes in the blood corpuscles above referred to are manifest.

I cannot better explain my views with reference to this affection than by quoting from an

article that I contributed to the *Philadelphia Medical Times* for April 3d, 1886. "The most interesting fact in connection with the examination of the blood of pernicious anæmia, and one to which, so far as I know, attention has never been particularly directed, is that it demonstrates a reversion to the type of blood found in the lower animals. This might be justly regarded as a fanciful idea if it were based upon a resemblance of the blood of pernicious anæmia to that of the lower animals—birds, fishes, reptiles—in any one particular; but I propose to show that the red corpuscles in this disease *approach* those of the lower animals in many, if not in all, of their chief characteristics; namely, in their number, their size, their shape, and the amount of hæmoglobin they carry." After giving some details concerning the blood corpuscles of the lower vertebrate animals and their percentage of hæmoglobin, I continued as follows: "Turning from these interesting facts of comparative physiology to their bearing upon the subject of this paper, we observe in well-marked cases of pernicious anæmia: 1. A reduction in the number of the red corpuscles to a degree that is normal in the

cold-blooded animals. It is not at all uncommon to find in this disease less than 1,000,000 corpuscles per cubic millimetre. My lowest counts have been 525,000 five days before death; 560,000 in a case in which recovery took place; and 315,000 a few hours before death. In the celebrated case of Quincke there were but 143,000 per cubic millimetre, and yet the patient recovered. Figures like these are, as has just been said, normal in the cold-blooded animals. 2. In pernicious anæmia the proportion of hæmoglobin is often much greater than normal. It has been observed by Laache and others to be double the normal amount. This, in the opinion of the writer, is the most remarkable feature of this disease, distinguishing it from all other forms of anæmia, and is due to the fact that—3, many, sometimes the majority, of the corpuscles are greatly increased in size. This is well seen in the accompanying cuts, from photo-micrographs of diseased and normal blood, made for me by Mr. W. H. Walmsley, of this city. The photographs of the two specimens were made under precisely similar optical conditions. The patient furnishing the diseased specimen of blood is a typical case of



pernicious anæmia, and is still under my observation.*

"By applying the points of a pair of compasses to the enlarged corpuscles, it will be proved that many of them are at least double the normal size. 4. The corpuscles are not only increased in diameter, but altered in shape, and have a decided tendency to assume an *oval* outline. So much so that, in measuring them in the manner indicated, we have to take into consideration the direction in which the measurement is made. *They have a long and a short diameter.*"

The specimen from which the above cut was taken was not selected with the view of upholding this theory of reversion, but may be regarded as typical of the corpuscles of pernicious anæmia. The enormous size of the corpuscles (megalocytes) and their altered shape are still better shown in a cut in the work of Laache (*Die Anæmie*), who had no theory of reversion to maintain.

From the standpoint of the blood changes and of the clinical history, I contend that pernicious anæmia is a condition that may result

* He has since died.

from a number of causes. Prominent among these is atrophy of the stomach. In the *American Journal of Medical Sciences*, April, 1886, I reported, in conjunction with Prof. Wm. Osler, a typical case of pernicious anæmia in which the only special lesion was atrophy of the mucous membrane of the stomach. "This was evident to the naked eye in the thin, cuticular appearance, and was abundantly confirmed by the microscopical examination, which showed that the peptic glands had been destroyed over the greater portion of the organ." About the same time I had under observation another case, a lady, whose symptoms and blood changes were identical with those of the above mentioned case. After an illness of more than a year she died, and at the autopsy, at which I was present, no lesion was found to explain the profound alteration of the blood. According to most authorities, the first of these cases in which a lesion was found, to which the symptoms might be reasonably attributed is, for that very reason, not a case of pernicious anæmia. The second case, on the other hand, is a case of pernicious, or "idiopathic," anæmia because a lesion, to which the symptoms might be attributed, was

not found. This appears to me to be a very unscientific mode of considering this subject. Little by little, causes have been discovered sufficient to account for all the symptoms of many cases of idiopathic anæmia. One of the latest contributions of this sort has been that of Dr. Gustav Reyher (*Deutsches Archiv für Klin. Med.*, Bd. xxxix), who reports thirteen cases of profound anæmia caused by an intestinal parasite, the bothriocephalus latus. In all their features, these cases deserve the name of pernicious, and had they been fewer in number and treated in a different manner, the anæmia might have been considered "idiopathic," the presence of a tapeworm in the intestine being regarded, in a country where this parasite is not uncommon, as a mere coincidence. The proof that the anæmia was secondary and parasitic was furnished by the fact that, in every instance, a wonderfully rapid recovery from an apparently hopeless condition followed the expulsion of the worm. From such facts as these it is reasonable to conclude that our ignorance concerning the cause of the most obscure forms of pernicious anæmia, and our expression of that ignorance by the term "idiopathic," will gradually disappear.

Having stated above that I do not regard pernicious anæmia as an independent disease, some explanation is needed of my reasons for classifying it under the head of primary anæmias. I have none better than the one already given by me in the course of an article in the *Medical News* for July 3d, 1886:—

"Opinions are divided as to whether pernicious anæmia is due to the operation of a cause (unknown) *sui generis*, or to the prolonged operation of the ordinary causes of anæmia. The writer is of the opinion that the varied clinical history of the different cases on record furnishes most decided evidence in favor of the latter view. Anæmia, once established, tends to perpetuate itself in that species of vicious circle of which so many examples are furnished by pathology. Thus, to take an extreme example, the epileptiform convulsions which immediately precede death from hemorrhage are due to cerebral ischæmia, and this very ischæmia is increased by the convulsions, for experiments have shown that the voluntary muscles contain a much greater amount of blood during contraction than while at rest. It is quite as essential to the blood-making organs

as it is to the nerve centres that they be properly supplied with blood, in order that they may act their important part toward maintaining the bodily health. Doubtless there are reserve powers and compensatory activities in each and all of the blood-making organs, which may suffice to furnish a fair quality of blood under the most adverse circumstances. These powers, however, have their limit, and, once exhausted, the anæmia, instead of continuing 'simple,' 'functional,' or 'symptomatic,' becomes 'essential,' 'organic,' or 'pernicious.' "

In short, I consider some forms of pernicious anæmia to be due to malnutrition of the cytogenetic organs.

Symptoms.—In the words of Coupland, "the symptoms of pernicious anæmia are those of simple anæmia aggravated and intensified." In well-marked cases the appearance of the patient is, to a certain extent, diagnostic. The lips and palpebral conjunctiva are of a milky white color and the skin of a lemon tint. This hue of the skin is characteristic, and at once gives rise to the suspicion of pernicious anæmia to those who have seen one or more cases of the disease. It is unnecessary to enter at length

into the symptoms of this affection which are, for the most part, dependent upon want of oxygen. The chief of them are extreme muscular prostration, breathlessness and syncope on slight exertion, or even in raising the head from the pillow; and digestive disturbances, such as anorexia, nausea and vomiting, and constipation alternating with diarrhœa. Insomnia is more frequent than drowsiness until toward the end, when somnolence gradually deepens into lethargy and coma. Physical examination, in typical cases, reveals nothing but anæmic murmurs over the heart, most distinct at the base and the *bruit de diable* in the veins of the neck. The pulse is usually rapid, from 100 to 120. The bones, particularly the sternum, are often tender on percussion. Retinal hemorrhages are found in the majority of cases. The blood is not only of the poorest quality, but is so small in quantity that often a drop is squeezed with great difficulty from a deep puncture in the finger pulp. It resembles serum more than blood, and is aptly compared to water in which beef has been washed. On examination with the microscope, the corpuscles present great diversities in size and shape. The majority are

often much larger than normal, and, compared with normal corpuscles, are worthy of the name of *megalocytes*. Others are much below the normal size, and are called *microcytes;* while others are greatly distorted, being pear-shaped for the most part, but sometimes biscuit-shaped, hammer-shaped, or anvil-shaped. These last are known as *poikilocytes*. The percentage of hæmoglobin, owing to the increased size of the corpuscles, is often as great as, or greater than, normal, sometimes attaining twice the normal proportion. This abnormal proportion of hæmoglobin is not always due to the increased size of the corpuscles alone; for, in some cases, the blood contains a large number of minute, highly-colored globules, which Eichhorst regarded as pathognomonic. They are so minute as to look like "small, red-tinged, fat globules." These bodies are, of course, not counted in estimating the number of the red corpuscles, and yet their coloring matter contributes to the estimate of the percentage of hæmoglobin. The corpuscles are, therefore, sometimes credited with more coloring matter than they possess. These minute colored bodies are not always present. I have met with them in but one case,

and Dr. Grainger Stewart was unable to find them in two well-marked and ultimately fatal cases which occurred in his practice. Fever of irregular type is certain to occur in late stages of pernicious anæmia. It has already been spoken of among the symptoms of anæmia in general. An increased excretion of nitrogen by the kidneys has been demonstrated in this affection by Strümpell, and is due to the inadequate supply of oxygen to the tissues. This fact is of interest in connection with the extensive fatty degeneration, which is sometimes the only lesion detected in this disease. "The fat represents the non-nitrogenized remnants of the decomposed albuminoids."

Anatomical Characters. — These are the changes in the blood itself and the consecutive lesions in other tissues. The former have been already described and figured in the course of this section Of the latter, the fatty degenerations of heart, intima of blood vessels, gastric tubules, etc., are mentioned under the head of anatomical characters of anæmia in general. In 1875, Prof. William Pepper suggested the marrow as the source of the blood lesions of pernicious anæmia, and "described definite

changes, chiefly of small, granular cells, in the marrow of the radius and sternum in one case." The marrow in this case, the first in which a careful examination of this tissue was made, is described as "decidedly paler than in health." This is not the appearance of the hyperplasia of the marrow, which is regarded by some as the fundamental lesion of this affection. The marrow is of a reddish purple color; its consistence is increased; its fat cells have disappeared, and the specific cellular elements of the medulla have increased in amount. Frequently, also, large numbers of nucleated red corpuscles are found. These changes, interesting and suggestive though they be, are by no means peculiar to pernicious anæmia and, when present, are not primary. They may be entirely absent, as in a thoroughly studied case reported by Dr. J. H. Musser, of Philadelphia. They may also be present in other diseases. They were found by Litten in four cases of uterine carcinoma, and by Orth in a case of carcinoma recti, and in another of carcinoma mammæ. (*Berlin Klin. Wochensch.*, xiv, 748.)

Diagnosis.—In accordance with the views here presented, an anæmia has entered upon

the pernicious stage when the blood corpuscles are greatly diminished in number — below 2,000,000 per cubic millimetre—and have undergone the alterations in size and shape already described and figured. In addition, the percentage of hæmoglobin may be normal or above normal; certainly but little below it in any case. A blood containing megalocytes, poikilocytes and microcytes, is the blood of pernicious anæmia. This condition may be secondary, *i. e.*, the cause is known; or primary, *i. e.*, the cause is, *as yet*, unknown.

Prognosis.—The prognosis of pernicious anæmia is unfavorable, but there are brilliant exceptions to this rule; for example, those furnished by Reyher's cases. These were, doubtless, from an etiological standpoint, cases of parasitic anæmia, but clinically they presented every feature of pernicious anæmia. In general terms, when the cause is known and removable, the prognosis is good; when known and not removable, it is hopeless; when unknown, it is doubtful.

Treatment.—Confining what is to be said about treatment to those cases in which the cause is unknown, the best results have been

attained by the use of arsenic, iron, and quinine. Numerous undoubted cures have followed the use of the first of these drugs, which may be given in pill or in Fowler's solution. Transfusion has been attended with little or no success, but Dr. Oscar Silbermann reports two cases of profound anæmia which recovered after subcutaneous injections of defibrinated blood. The blood was injected under strict antiseptic precautions, and the quantity of each dose varied from twenty to forty grammes. Inhalations of oxygen and the subcutaneous injection of quinine are recommended by Dr. Henrot of Rheims. Of equal importance with drugs, is a nutritious diet, of which the digestion may be assisted by malt and pancreatic extract or the food may be peptonized before its ingestion.

SECONDARY ANÆMIA.

As already remarked on a previous page, "Nearly every morbid process, when it occurs in a severe form, is sooner or later followed by anæmia." It is therefore impossible, within the limits of this work, to consider every form of secondary anæmia. It is also unnecessary, for

the differences between the various forms are those of degree, not of kind.

The anæmias of fever and hemorrhage have already been considered. That of syphilis has been studied by Wilbouchewitch; by Keyes, of New York, and by Laache, of Christiania, and it has been demonstrated that the improvement which follows the administration of mercurials is accompanied with an increase in the number and value of the red corpuscles. In the advanced stages of phthisis, cancer, Bright's disease, and cirrhosis of the liver, the blood corpuscles are greatly reduced in number—between 2,000,000 and 3,000,000—and may assume the characters—increased size and altered shape—of pernicious anæmia.

TOXANÆMIA.

A poison may produce anæmia either directly or indirectly. The ingestion of arsenic and phosphorus, and the inhalation of arseniureted hydrogen are directly followed by the destruction of red corpuscles in such quantities that hæmoglobin appears in the urine, and even jaundice (hæmatogenous) may ensue. In certain susceptible individuals the same symp-

toms are caused by prolonged exposure to cold. Other substances, such as potassium chlorate and certain edible fungi, morchella and helvella, esculenta, produce the same effects. For details concerning these and other agents destructive to the red corpuscles, the reader is referred to my article on "Hæmoglobinuria," in "Wood's Reference Handbook of Medicine." The action of lead upon the blood corpuscles is probably altogether indirect, through the marked disturbances of digestion to which it gives rise. A decided degree of anæmia in a case of chronic lead poisoning should lead to a careful examination of the urine; for, as is well known, the long-continued ingestion of lead is one of the causes of cirrhotic kidney.

The anæmia, if such it can be called, produced by carbonic oxide poisoning, differs from all other forms of toxanæmia. This gas, when inhaled, "displaces the oxygen of the blood-coloring matter, and takes its place, molecule for molecule. The combination thus formed is remarkable for its stability, although, contrary to what was formerly supposed, it can be displaced by an indifferent gas or in a vacuum. Its crystals are isomorphous with those of oxy-hæmo-

globin, but have a slight bluish tinge. Its spectrum is almost identical with that of O-hæmoglobin, but the two absorption bands are moved very slightly nearer the violet end."* The effect of this gas is to *paralyze* the red corpuscles which, until it is displaced, are incapable of performing their functions. The symptoms of this form of toxanæmia are coma, with stertorous respiration, pallor and coolness of the skin, while the mucous membranes are bright red; rigidity of muscles, dilated pupils and usually a slow, easily-compressible pulse. The symptoms are, however, not uniform; for cases are reported in which there was no stertor, the pulse was small and quick and the pupils contracted. Convalescence is apt to be very slow.

In a case reported by Dr. John Graham in the "Transactions of the College of Physicians of Philadelphia," series iii, vol. viii, the patient, a woman, æt. 74, was not able to sit up until seventy-three days after the accident.

PARASITIC ANÆMIA.

The parasites which have been thus far recog-

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*Article on Blood, in "Wood's Reference Handbook," by F. P. Henry.

nized as causative of anæmia are the anchylostomum duodenale, the bilharzia hæmatobia, the filaria sanguinis, the bothriocephalus latus, and perhaps, also, the plasmodium malariæ.

The anchylostomum duodenale was first recognized by Griesinger, in 1854, as the cause of a profound endemic anæmia, known as Egyptian chlorosis. Since then it has attacked the Italian laborers employed in the construction of the St. Gothard tunnel, and has also prevailed among brickmakers in Germany. The bilharzia, first discovered by Bilharz in Egypt, in 1851, gives rise to anæmia by the hæmaturia caused by its presence in the body. The adult animals lie in dilated blood vessels in the neighborhood of the bladder or other urinary outlet, and the symptoms are due to the interference with the circulation and the irritation caused by the ova on their way to the urinary passages. The filaria sanguinis causes anæmia by interfering with the lymphatic circulation. The obstruction to the lymph vessels may be so great as to lead to their rupture, in which event the lymph escapes from the body, usually with the urine (chyluria); sometimes, however, directly from the integument, as in cases of lymph-scrotum.

This parasite is quite common in certain tropical and subtropical countries, especially in China, and has recently acquired a new interest from the discovery, by Dr. John Guiteras, of Charleston, S. C., that it is indigenous to the United States.*

The plasmodium malariæ is the hæmatozöon discovered by Laveran in Algiers. It exists within the red corpuscles and free in the blood, and is probably operative in the causation of malarial anæmia. This organism has been studied by several careful observers; in this country particularly by Councilman,† of Baltimore, and Osler,‡ of Philadelphia, although, to quote the latter, "Laveran's original description is well nigh complete, and subsequent workers have done little else than confirm his results, though to Marchiafava and Celli is due the credit of insisting upon the amœboid character of the intra-cellular form."

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* *Medical News*, April 10th, 1886.

† "Transactions of the Association of American Physicians," vol. i.

‡ *British Medical Journal*, March 12th, 1887.

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